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CARDIAC EFFECTS OF AMODIAQUINE AND SULFADOXINE-PYRIMETHAMINE IN MALARIA-INFECTED AFRICAN PATIENTS

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Abstract. The cardiac effect of amodiaquine and sulfadoxine-pyrimethamine was studied in adult Cameroonian patients with acute uncomplicated *Plasmodium falciparum* malaria by electrocardiographic monitoring over the course of 7 days. Clinical and parasitological responses were monitored until Day 14. Bradycardia was observed in 16 of 20 amodiaquine-treated patients on Day 2, which corresponds to the time when maximal cumulative plasma concentration is reached, and in 12 of 20 patients on Day 7. A bradycardic effect lasting several days was not noted in patients treated with sulfadoxine-pyrimethamine. Significantly prolonged P, PQ, QRS, and QTc intervals were recorded on Day 2 after both 30 and 35 mg of amodiaquine base per kilogram of body weight had been administered, but these intervals were not correlated with the plasma monodesethylamodiaquine (main human active metabolite of amodiaquine) level. Electrocardiographic changes after therapy with sulfadoxine-pyrimethamine were minor and transient. All patients had fever and parasite clearance on or before Day 3 and remained free of fever and parasites until Day 14. None of the patients complained of cardiovascular adverse effects during the follow-up. These results suggest the absence of significant cardiac effects of amodiaquine and sulfadoxine-pyrimethamine at usual therapeutic doses, but they should draw the attention of clinicians treating malaria-infected patients who have taken other antimalarial drugs with cardiovascular side effects or those who are under treatment with cardiovascular drugs.

INTRODUCTION

The spread of chloroquine-resistant *Plasmodium falciparum* malaria has led to an increasing use of amodiaquine as an alternative first-line drug for uncomplicated infections in Cameroon.[1] The World Health Organization (WHO) has adopted contradictory positions on the use of amodiaquine as a result of serious hematologic and hepatic adverse reactions observed in tourists who are taking chemoprophylaxis.[2,3] However, several recent clinical studies suggest that adverse reactions are rare when amodiaquine is administered for treatment.[4–6] In addition, these studies have shown that amodiaquine retains a high efficacy against *P. falciparum* infections in chloroquine-resistant endemic areas in east and central Africa. The clinical efficacy and relative safety of amodiaquine for therapeutic use, even in young children, together with its low cost, explain the continued use of this drug in some African countries.

Amodiaquine is a Mannich base derivative and an analog of chloroquine. It has been used since the 1940s. Despite its long use, the pharmacodynamic properties of amodiaquine, including electrocardiographic effects, have not been extensively studied in humans. Other antimalarial drugs containing the quinoline nucleus, including chloroquine, quinine, quinidine, and halofantrine (a phenanthrene amino alcohol derivative), are known to prolong ventricular repolarization, which is evidenced by increased QTc interval in electrocardiogram, at usual therapeutic concentrations.[7–9]

Although symptomatic cardiac effects have not been reported after administration of 4-aminoquinolines,[9,10] the electrocardiographic changes produced by chloroquine in healthy volunteers and malaria-infected patients are of potential concern in areas where amodiaquine is extensively used because of the similarities in chemical structures and properties of chloroquine and amodiaquine. In this study, we investigated the electrocardiographic effects of amodiaquine in symptomatic, malaria-infected patients and correlated these changes with plasma concentrations of amodiaquine and those of monodesethylamodiaquine, the biologically active metabolite of amodiaquine. We also investigated whether a sulfadoxine-pyrimethamine (SP) combination produces electrocardiographic changes in patients.

PATIENTS AND METHODS

Symptomatic Cameroonian adult patients who sought treatment at the Nlongkak Catholic missionary dispensary were enrolled in the study if the following criteria were met: monoinfection with *P. falciparum*, age $\geq$ 15 years, and negative Saker-Solomon's urine test.[11] Pregnant women and patients with signs and symptoms of severe and complicated malaria were excluded from the study.[12] Patients were also excluded if the initial physical examination or if the baseline electrocardiogram revealed abnormal or pathological cardiovascular features. The study was approved by the ethics committee of the Faculty of Medicine, University of Yaoundé I, and Cameroonian Ministry of Public Health.

After informed consent was obtained, patients were randomly assigned to 1 of 3 regimens. The first regimen (AMQ30) comprised orally administered amodiaquine at a total dose of 30 mg per kilogram of body weight of amodiaquine base, administered in 3 equal doses (10 mg/kg) on Days 0, 1, and 2. The second regimen (AMQ35A) was a total dose of 35 mg/kg, administered in 4 doses as follows: 10 mg/kg at Hour 0 and 5 mg/kg at Hour 6 on Day 0, then 10 mg/kg on Days 1 and 2. The third regimen (AMQ35B) was a total dose of 35 mg/kg, administered in 4 doses as follows: 7.5 mg/kg at Hour 0 and 7.5 mg/kg at Hour 6, and 10 mg/kg on Days 1 and 2. These 3 regimens were evaluated because there is currently no consensus regarding the dosage schedule of amodiaquine. In another nonrandomized study, the fourth group of patients who met the inclusion criteria

TABLE 1
Clinical and laboratory parameters in patients before malaria treatment*

Characteristic	Amodiaquine, 30 mg/kg (n = 11)	Amodiaquine, 35 mg/kg (n = 9)	Sulfadoxine-pyrimethamine (n = 8)
Age (years)	28.0 ± 8.8 (18–43)	26.6 ± 6.0 (16–32)	35.3 ± 17.2 (16–62)
Weight (kg)	70.0 ± 20.2 (50–124)	62.0 ± 10.0 (47–82)	65.1 ± 6.0 (55–70)
Hematocrit (%)	40.0 ± 6.9 (30–53)	40.7 ± 6.6 (26–48)	39.5 ± 8.3 (28–53)
Temperature (°C)	37.9 ± 1.0 (36.5–39.5)	38.0 ± 1.3 (36.0–40.5)	37.8 ± 0.5 (37.0–38.5)
Parasite density (parasites/μL)	2,600 (140–98,000)	3,160 (18–206,000)	890 (120–13,100)

* Values are expressed as mean ± standard deviation (range). Parasite density is expressed as the geometric mean (range).

and who denied history of allergic reactions to sulfonamides was treated with a single orally administered dose of SP. Each dose was administered under supervision, and patients were observed for at least 1 hr after drug intake. The only other drug that the patients received until Day 7 was paracetamol, which was administered for fever or headache.

Patients were followed on an outpatient basis on Days 1, 2, 3, 7, and 14. This follow-up schedule was based on the new WHO protocol for monitoring the therapeutic and parasitological response to antimalarial drugs.[13] During each visit, a complete physical examination and a thick blood film examination were performed. In addition to these follow-up visits, patients assigned to regimens AMQ35A and AMQ35B received a home visit 6 hr after the first dose for the administration of the second dose under supervision and received an additional examination 10 hr after the first dose. Baseline electrocardiogram (Cardiovit AT-3/1 3-channel electrocardiograph for 12 simultaneous leads; Schiller AG, Baar, Switzerland) was performed before the first dose. In patients assigned to the AMQ30 regimen, serial electrocardiographic monitoring was performed at Day 0/Hour 4, Day 2/Hour 4, Day 3, and Day 7. In patients assigned to either the AMQ35A or AMQ35B groups, electrocardiogram was monitored at Day 0/Hour 10, Day 2/Hour 4, Day 3, and Day 7. For SP-treated patients, an electrocardiogram was performed 4 hr after the single dose, and subsequent electrocardiograms were recorded on Days 1, 2, 3, and 7. Electrocardiographic intervals were measured automatically by the apparatus and checked to ensure accuracy.

Venous blood samples (5 mL) were collected into ethylenediamine tetraacetic acid-coated tubes before the first dose on Day 0 and 4 hr after the first dose (for AMQ30 regimen and SP) or 10 hr after the first dose, corresponding to 4 hr after the second dose (for AMQ35A and AMQ35B regimens). These time points were chosen for blood sampling and electrocardiographic monitoring because they correspond to the average time to attain peak plasma concentrations of monodesethylamodiaquine, sulfadoxine, and pyrimethamine on Day 0.[14,15] Likewise, the Day 2/Hour 4 sample corresponds to the maximal cumulative monodesethylamodiaquine plasma concentration. Blood samples were immediately centrifuged at 2,000 rpm for 10 min, and plasma was stored at −80°C. Plasma concentrations of amodiaquine, monodesethylamodiaquine, sulfadoxine, and pyrimethamine were measured by high-performance liquid chromatography with ultraviolet detection.[16,17]

Pretreatment clinical and laboratory findings were compared by Student's t-test. Various electrocardiographic intervals were compared before and after treatment by the Wilcoxon signed rank sum test. Data from patients in the AMQ35A and AMQ35B groups were grouped and compared with those assigned to the AMQ30 regimen by the Mann-Whitney rank sum test. The Spearman rank correlation test was used to correlate QTc intervals with plasma monodesethylamodiaquine levels. Between-group analysis of amodiaquine- and SP-treated patients was not performed because the patients were not assigned randomly to one of the 2 drugs. In all cases, 2-tailed tests of significance set at 5% were calculated.

RESULTS

Of 23 patients enrolled in the amodiaquine study, 3 were lost to follow-up (2 from the AMQ30 group and 1 from the AMQ35B group). In the SP study, 9 patients were enrolled, but one was lost to follow-up. The baseline clinical and laboratory characteristics are presented in Table 1. All parameters were similar ($P > 0.05$) between the combined group, AMQ35A and AMQ35B, and AMQ30 group. The nonrandomized SP group had slightly higher mean ages and lower initial parasite densities. All patients had parasite and fever clearance on or before Day 3 and remained aparasitemic and apyretic until Day 14. None of the patients complained of cardiovascular adverse effects.

A prominent effect was observed in the heart rate of amodiaquine-treated patients. At 4–10 hr after treatment, a slightly lower heart rate was recorded (Figure 1). Bradycardia was observed after both 30 mg/kg and 35 mg/kg amodiaquine treatment from Day 2 to Day 7. Only one patient was bradycardic (55 beats/min) before treatment. On Day 2 and Day 3, 14 and 16 of 20 amodiaquine-treated patients had bradycardia, respectively (range, 43–59 beats/min). On Day 7, 12 of 20 patients still had bradycardia (range, 50–59 beats/min). In the SP group, there was a decrease ($P < 0.05$) in heart rate 4 hr after treatment, and the heart rate remained relatively constant until Day 7. Bradycardia was observed in 2 SP-treated patients on Day 3 (56 and 59 beats/min) but resolved on Day 7 (68 and 66 beats/min, respectively).

The other electrocardiographic data are summarized in Table 2. Comparison of baseline and 52-hr posttreatment values in 20 amodiaquine-treated patients showed a significant prolongation of P, PQ, QRS, and QTc intervals ($P < 0.05$). There was no statistical difference ($P > 0.05$) between AMQ30 and AMQ35 regimens. The QTc intervals were above the upper limit of normal values (440 msec) in 2 patients before treatment. These 2 patients had prolonged QTc until Day 3 or 7. A total of 7 (range, 448–506 msec) and 3 (range, 463–483 msec) patients had abnormally prolonged

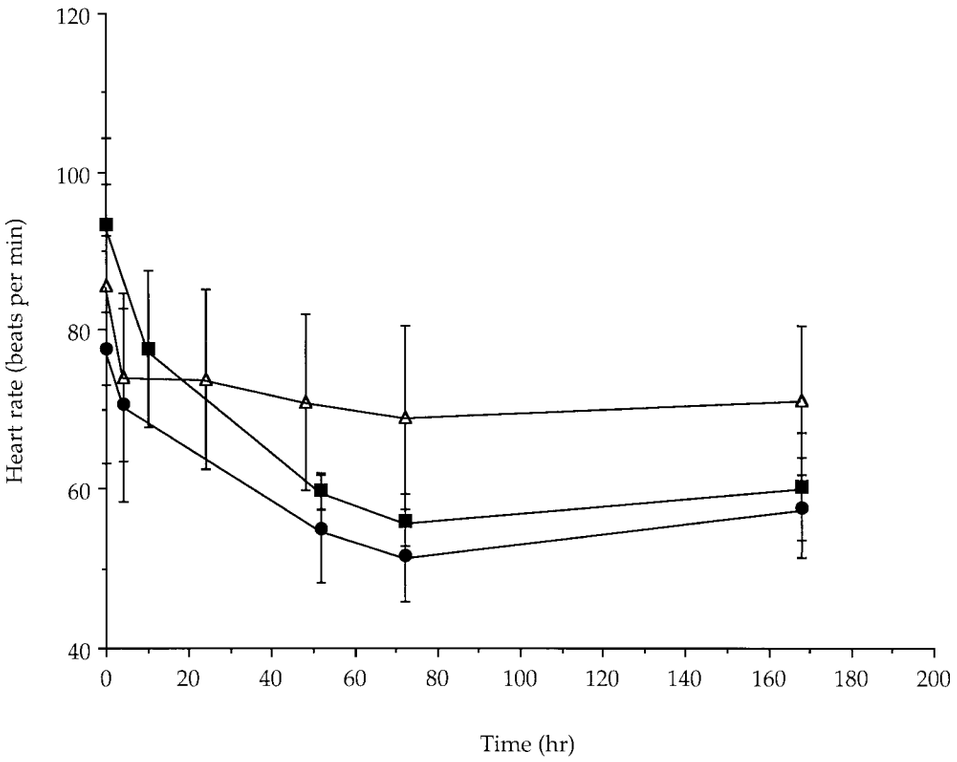

FIGURE 1. Change in heart rate in malaria-infected patients treated with 30 mg/kg **(filled circle)** or 35 mg/kg **(filled square)** of amodiaquine base in 3 or 4 divided doses or a single dose of sulfadoxine-pyrimethamine **(open triangle).** Heart rate was measured automatically with an electrocardiographic monitor.

TABLE 2

Electrocardiographic parameters before and after amodiaquine (AMQ) and sulfadoxine-pyrimethamine (SP) treatment in malaria-infected patients

	Time after the first dose†						
Parameter*	Day 0, Hour 0	Day 0, Hour 4	Day 0, Hour 10	Day 1	Day 2	Day 3	Day 7
P wave							
AMQ 30	112.8 ± 11.1	123.3 ± 10.6	–	–	129.6 ± 21.1	144.0 ± 42.1	116.1 ± 12.7
AMQ 35	107.9 ± 11.2	–	118.4 ± 9.0	–	125.7 ± 6.4	118.8 ± 7.0	117.2 ± 7.6
SP	110.6 ± 10.9	127.8 ± 23.0	–	110.9 ± 19.3	116.5 ± 12.2	118.2 ± 18.5	115.2 ± 12.5
PQ interval							
AMQ 30	165.6 ± 26.1	173.4 ± 21.3	–	–	180.9 ± 29.3	192.5 ± 43.6	171.4 ± 29.4
AMQ 35	152.7 ± 23.6	–	169.4 ± 25.1	–	177.4 ± 20.8	169.2 ± 17.7	163.3 ± 18.8
SP	153.1 ± 15.8	171.6 ± 66.9	–	155.4 ± 27.6	160.5 ± 16.8	164.5 ± 13.2	164.0 ± 12.8
QRS interval							
AMQ 30	90.9 ± 14.0	103.8 ± 17.2	–	–	107.2 ± 16.0	125.7 ± 64.7	99.6 ± 14.5
AMQ 35	97.8 ± 16.8	–	107.4 ± 15.5	–	118.1 ± 22.6	108.7 ± 15.9	106.2 ± 24.1
SP	101.1 ± 33.8	110.8 ± 46.1	–	125.6 ± 85.6	97.6 ± 11.8	102.8 ± 27.4	96.4 ± 14.3
QTc interval							
AMQ 30	383.6 ± 32.6	403.4 ± 29.7	–	–	412.9 ± 39.0	394.6 ± 31.8	391.2 ± 32.8
AMQ 35	408.2 ± 17.3	–	418.2 ± 41.4	–	443.9 ± 42.0	421.7 ± 35.9	394.7 ± 13.7
SP	420.1 ± 34.6	426.2 ± 25.9	–	440.2 ± 60.6	417.5 ± 20.8	415.6 ± 36.5	412.5 ± 23.7

* Electrocardiogram in patients treated with amodiaquine, either 30 mg per kilogram of body weight (AMQ 30) or 35 mg/kg body weight (AMQ 35, including AMQ35A and AMQ35B treatment regimens), or with sulfadoxine-pyrimethamine.

† The electrocardiographic intervals (mean ± standard deviation) are expressed in milliseconds. Day 2 data were obtained 4 hr after the last orally administered dose of amodiaquine, which corresponds to the maximal cumulative plasma concentration of monodesethylamodiaquine. The corresponding peak concentration occurs about 4 hr after the single SP dose (Day 0, Hour 4). At these 2 time points for the corresponding drugs, a significant decrease ($P < 0.05$) in heart rate was observed in AMQ- and SP-treated patients, and a significant prolongation ($P < 0.05$) of P, PQ, QRS, and QTc intervals was observed in AMQ groups. There was no statistical difference ($P > 0.05$) between AMQ30 and AMQ35 regimens.

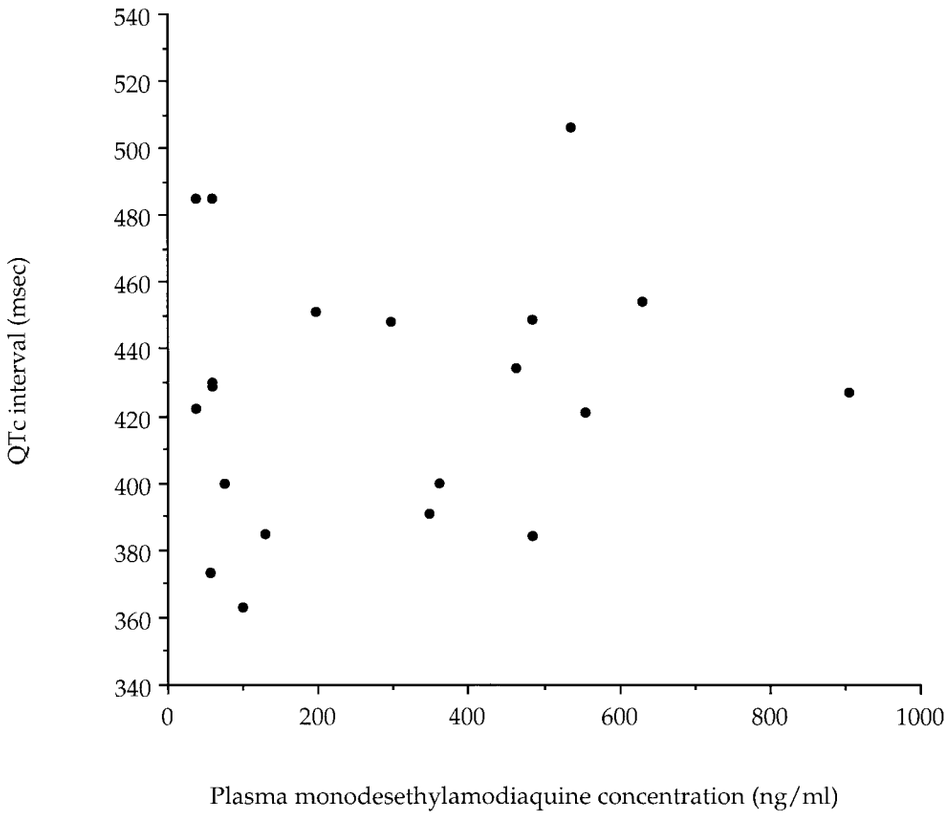

FIGURE 2. The QTc interval and plasma concentration of monodesethylamodiaquine measured 52 hr after treatment. This time point corresponds to the mean maximal, cumulative plasma concentration of monodesethylamodiaquine. There was no correlation between the plasma monodesethylamodiaquine concentration and QTc interval at 52 hr after treatment ($r = 0.111$; $P > 0.05$; shown in the figure) or change in QTc interval from baseline ($r = 0.081$; $P > 0.05$; data not shown).

QTc (> 440 msec) on Day 2 and on Day 3, respectively. Only one patient, who had a prolonged QTc interval before treatment, still had a prolonged QTc interval on Day 7 (472 msec). Monodesethylamodiaquine was not detected in any of the pretreatment plasma samples. Amodiaquine, the parent compound, was detected in 2 patients in the AMQ35B group 4 hr after the second oral dose (Day 0/Hour 10). Plasma monodesethylamodiaquine concentration was not correlated with the QTc interval on Day 2/Hour 4 ($r = 0.111$; $P > 0.05$) (Figure 2).

Among patients treated with SP, Patient 1 had a QTc interval near the borderline level (421 msec) before treatment and had prolonged QTc interval until Day 7 (range, 443–453 msec), whereas Patient 2, with a prolonged QTc interval before treatment (499 msec), showed a prolonged interval until Day 3 (range, 441–488) and a normal interval on Day 7 (429 msec). Four hours after drug intake, plasma concentrations of sulfadoxine and pyrimethamine were 59 μg/mL and 155 ng/mL in the first patient, respectively, and 135 μg/mL and 475 ng/mL in the second patient, respectively. Because the ranges of plasma concentrations of sulfadoxine and pyrimethamine in 8 SP-treated patients were 59–205 μg/mL and 155–750 ng/mL, respectively, there was no apparent relation between plasma drug concentrations and QTc prolongation in these 2 patients.

DISCUSSION

The unexpected discovery of cardiotoxicity of halofantrine several years after its availability on the market and subsequent reports of its potentially fatal adverse cardiovascular effects emphasize the need for thorough investigation of cardiac effects of antimalarial drugs.[8,18–20] Quinine and quinidine are known to affect the atrioventricular conduction system, leading to delayed ventricular repolarization.[7,21] Mild and transient prolongation of QTc interval may occur at the therapeutic or prophylactic orally administered dose of chloroquine, mefloquine, and lumefantrine but seems to be of no clinical significance.[9,10,22,23] Therapeutic dose of artemisinin derivatives may induce transient first-degree atrioventricular heart block in rare cases, but it is currently held that these drugs do not have any clinically significant cardiac effects.[24,25] Cardiac effects have not been reported with other drugs used in antimalarial chemotherapy, including antifolate drugs, atovaquone, pyronaridine, and antibiotics.

In previous electrocardiographic studies, it has been reported that sinus bradycardia may be observed frequently in patients treated with amodiaquine, with or without SP.[26] The results of our study are in agreement with this observation. Sinus bradycardia and sinus arrhythmia also occur frequently (up to 68%) in patients treated with mefloquine, chloroquine, halofantrine, and artesunate.[8,27,28] Amodiaquine possesses an

anti-inflammatory and antipyretic effect, like chloroquine, and it may be hypothesized that fever clearance due to specific antimalarial treatment and simultaneous treatment with paracetamol may be associated with lower heart rate. This hypothesis is consistent with the diminished heart rate, as compared with the baseline values, after SP and paracetamol treatment in our study. However, all patients were not febrile at the time of enrollment in our study. In addition, bradycardia may be observed in healthy tourists on mefloquine prophylaxis and is therefore not exclusively related to defervescence during antimalarial treatment. The possible origin of sinus bradycardia in malaria-infected patients treated with antimalarial drugs is thus not clear at present.

In our study, we have observed other electrocardiographic changes that were not reported in earlier clinical studies on amodiaquine. In general, minor prolongation in P, PQ, and QRS intervals was observed after amodiaquine and SP treatment at the time when maximal cumulative plasma concentrations of the drugs were attained. More pronounced effect was seen in heart rate and QTc interval, especially after amodiaquine treatment. Taken together, the electrocardiographic effects of amodiaquine mimic to some extent those of quinidine and other class IA antiarrhythmic agents (disopyramide and procainamide), which block the sodium channel. Although sinus bradycardia seems to be frequent, a clear-cut relationship between plasma concentration of monodesethylamodiaquine and other electrocardiographic changes was not found. With other antimalarial drugs with known potential of QTc prolongation, electrocardiographic changes are dose dependent.[7,8] The lack of correlation between concentration and effect on ventricular conduction in our study may be due to a limited number of time points studied, a relatively small sample size, wide interindividual variations in pharmacokinetics and pharmacodynamics, absence of a significant and consistent effect of amodiaquine on ventricular depolarization and repolarization, or possible interfering effects of malarial disease itself on cardiac conduction.[29]

None of the patients complained of cardiovascular adverse effects in the present study or in our previous clinical studies in Cameroon.[6] Despite some concern raised by electrocardiographic changes induced by chloroquine,[9,10] the similarity in chemical structure in itself between chloroquine and amodiaquine does not predict similar adverse effects. Thus, amopyroquine, a close analog of amodiaquine, did not exhibit any significant electrocardiographic changes in healthy volunteers.[30] Until more evidence is available, amodiaquine can be safely prescribed to most patients with acute uncomplicated falciparum malaria, with the possible exception of patients with known congenital prolonged QTc syndrome.

Further studies are needed to evaluate the safety of amodiaquine in patients who have recently taken other antimalarial drugs with cardiovascular effects (quinine, quinidine, halofantrine, and mefloquine) and in those who are under treatment with cardiovascular drugs, such as digoxin, beta-blockers, and other antiarrhythmic agents. Moreover, because combination therapy is currently being advocated by many investigators to combat against multidrug-resistant *P. falciparum*,[31,32] cardiac evaluation of different drug combinations is necessary to ensure the safety of drug combinations.

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