THE EFFECTS OF ANTIMALARIAL DRUGS ON VENTRICULAR REPOLARIZATION


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Abstract. Cardiotoxicity has become a major concern during treatment with antimalarial drugs. Lengthening of the QTc and severe cardiac arrhythmia have been observed, particularly after treatment with halofantrine for chloroquine-resistant Plasmodium falciparum malaria. The purpose of this prospective study was to evaluate whether antimalarial agents alter dispersion of the QTc and ventricular repolarization dynamicity. Sixty patients with uncomplicated falciparum malaria were randomly allocated in four groups of 15 patients and treated with quinine, mefloquine, artemether, or halofantrine at recommended doses. Patients in treatment groups were compared with a group including 15 healthy controls with no history of malaria and/or febrile illness within the last month. QTc dispersion was measured on surface electrocardiograms. Repolarization dynamicity was analyzed from Holter recordings, which allow automatic beat-to-beat measurement of QT and RR intervals. Plasma drug concentration was determined by reversed-phase high-performance liquid chromatography. No change in QTc dispersion was observed after treatment with quinine, mefloquine, or artemether. Treatment with halofantrine was followed by a significant increase in QTc dispersion at 9 hours (P < 0.0001) and 24 hours (P < 0.01). Assessment of QT heart rate variability by QT/RR nychthemeral regression slope demonstrated no significant difference between the artemether (mean ± SEM = 0.170 ± 0.048), mefloquine (0.145 ± 0.044), and the control groups (0.172 ± 0.039). A significant increase in the Q-R/RR slope was observed in the quinine group compared with the control and artemether groups (0.135 ± 0.057; P < 0.04). With halofantrine, a significant increase in the QT/RR regression slope (0.289 ± 0.118) was observed (P < 0.0002). QTc interval, QT dispersion, and QT slope regression were significantly correlated with halofantrine and quinine plasma concentration. Mefloquine and artemether did not alter ventricular repolarization. Quinine induced a significant decrease in QT/RR slope of the same order of magnitude as those previously observed with quinidine. Both QTc dispersion and QT/RR slope were significantly modified by halofantrine. These repolarization changes were related to a class-III antiarrhythmic drug effect and may explain the occurrence of ventricular arrhythmia and/or sudden deaths reported after halofantrine intake.

INTRODUCTION

Over the last decade, several reports have raised the issue of cardiotoxicity associated with drugs currently used to treat Plasmodium falciparum malaria. Severe ventricular arrhythmia and sudden death have been observed in patients treated with halofantrine.1,2 Adverse cardiac effects have also been reported after treatment with other aryl-amino-alcohol agents such as quinine and mefloquine.3-5 QT prolongation observed with these agents was initially related to a quinidine-like effect. In every previous studies of the cardiac effects of antimalarial agents, the QT interval measured on a surface electrocardiogram (ECG) was considered a marker for screening unwanted cardiac disturbances, as well as to study the factors and clinical conditions that predispose to their occurrence. However, several findings suggest that lengthening of the QT interval is not a necessary and sufficient predictor of drug-associated cardiotoxicity. One problem with QTc interval measurement involves variability, not only in the same individual, but also in function of lead selection.6-7 Another problem is the absence of a reliable QTc lengthening cut-off to predict torsades de pointes.8 Finally, there is considerable overlapping between patients who develop drug-related torsades de pointes and patients treated uneventfully with the same drugs.9-10

In recent years, QTc dispersion and/or repolarization dynamicity appear to be more reliable predictors of drug-induced torsades de pointes.11,12 The aim of this study was to use these two methods to assess the effects of different antimalarial agents on the QT interval in patients treated for uncomplicated falciparum malaria. QTc dispersion measures interlead variations of QT interval duration. Since QTc dispersion is believed to reflect the inhomogeneity of ventricular repolarization, it may provide an indirect marker for identifying patients prone to ventricular arrhythmia. Ventricular repolarization dynamicity or QT frequency dependency is defined as the variation of QT interval with increasing heart rate. Study of repolarization dynamicity based on automatic measurements of QT interval and its related heart rate by ambulatory Holter ECG recording allows detection of heterogeneity in ventricular repolarization.12

MATERIALS AND METHODS

Patients. This study was carried out between May and August 1999 in 60 patients admitted for febrile illness to the Armed Forces School Hospital in Bouake, Côte d’Ivoire. Bouake is located in a P. falciparum multidrug-resistant area. Diagnosis of uncomplicated falciparum malaria was confirmed by Giemsa-stained thick and thin blood films.

Patients were randomly allocated into four groups of 15 patients for treatment with quinine, artemether, mefloquine, or halofantrine. Treatment regimens were as follows: quinine, 25 mg/kg/day administered orally in three doses for five days; artemether, 160 mg administered intramuscularly in two doses 12 hours apart on day 1, followed by 80 mg/day for four days; mefloquine, 1,500 mg administered in three equally spaced doses over a 24-hour period; and halofantrine, 1,500 mg/day administered in three equally spaced doses two hours after meals over a 24-hour period.

Blood samples were collected for a complete blood count and serum biochemistry before treatment. Parasite counts were made on thick blood films. The number of asexual parasites per 400 white blood cells was counted and multiplied by 20 to give an estimated count per microliter.
Exclusion criteria were clinical and/or biological signs of severe malaria,13 concomitant illness, recurrent vomiting or diarrhea, cardiovascular event history, antimalarial treatment within the 24 hours preceding admission, and ionic imbalance (hypokalemia and/or hypocalcemia). Patients in treatment groups were compared with a group of 15 healthy controls with no history of malaria and/or febrile illness within the last month. The study protocol was approved by the Ethics Committee of the Ministry of Health (Abidjan, Côte d’Ivoire).

Written informed consent was obtained from all patients.

**Electrocardiographic investigations.** A 12-lead ECG was recorded for all patients upon admission prior to treatment (H0) and at nine (H9) and 24 hours (H24) after the start of treatment. All electrocardiograms were recorded at paper speeds of 25 and 50 mm/sec and with a sensitivity of 10 mm/mV.

The QT intervals were measured using lead V2 from the onset of the QRS complex to the end of the T wave, defined as return of the terminal limb to baseline. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. The QT interval corrected for heart rate (QTc) was calculated according to Bazett’s formula, i.e., QTc = QT / \sqrt{RR} (the RR interval is defined as the time interval between the peaks of two consecutive R waves). A QTc value of 440 msec was considered the normal upper limit of QTc.8,9 The QTc dispersion defined as the difference between the longest and shortest QTc interval measured on the 12 standard leads was calculated at H0, H9, and H24 by two independent experienced observers. Electrocardiograms not allowing measurement of QTc dispersion in at least nine of the 12 leads were excluded from analysis. Based on previous studies, patients with QTc dispersion values greater than 65 msec were considered as being at risk for cardiac arrhythmia.10,14

Both patients and controls underwent 24-hour ambulatory Holter ECGs using a three-channel recorder (Sherpa III; Reynolds, Herdfordshire, United Kingdom) with three bipolar thoracic leads in a pseudo-orthogonal configuration (X, Y, Z). Recording was started on the day of treatment (between 9:00 AM and noon) for each patient and control subject. The ECG recordings were converted to digital format at a sampling rate of 128 Hz with a resolution of 10 bits using the Pathfinder 600 analysis system (Reynolds). Recordings with abnormally long intervals, severe artifacts, undetectable T waves, intermittent atrial fibrillation, and recording disturbances induced by sweating or chest movements were discarded. Beat-to-beat QT and associated RR intervals were automatically measured and averaged every 30 beats. The following parameters were studied: QT duration, defined as the distance between the onset of the Q wave and end of the T wave (Q–Tc, msec; the end of the T wave was defined as the point of intersection of the tangent to the steepest point of the downslope with the isoelectric line); RR interval; and QT plots versus RR interval.

The Q–Tc/RR data fitted a linear relationship15 and the regression slope of the Q–Tc/RR relationship defined the rate-dependence of the QT interval. The Q–Tc/RR slope was evaluated over a 24-hour period. Only tapes with a minimum 18-hour recording time and 90% analyzable QT intervals were considered valid. Mean ± SEM Q–Tc/RR was compared between patients and controls.

**Plasma collection and drug assay.** Venous blood samples (10 ml) were collected from an antecubital vein into heparinized tubes. Plasma was immediately separated by centrifugation and frozen at –80°C pending analysis. In patients treated with quinine, mefloquine and halofantrine, blood sampling was performed immediately prior to drug delivery and then at 9, 12, and 24 hours after intake. In patients treated with arte- meter, an additional sample was collected three hours after the first dose. Plasma concentrations of quinine, halofantrine, N-desbutyl-halofantrine, and mefloquine were determined by reversed-phase high performance liquid chromatography (HPLC) with ultraviolet detection after solid-phase extraction. Plasma concentration of arteether and its O-dealkylated metabolite dehydroartemisinin (DHA) were determined by HPLC method using reductive electrochemical detection.16

**Statistical analysis.** Results are expressed as mean values ± SEM. Statistical comparison of data was performed with a commercially available software program (STATVIEW®; Abacus Concepts, Inc., Berkeley, CA). Groups were compared by analysis of variance followed by a Bonferroni-Dunnet test if significant differences were found. The QTc/RR slopes were compared by a Mann-Whitney U test. Two-way analysis of variance with interaction and repeated measures was used to compare plasma drug data. A P value < 0.05 was considered statistically significant.

**RESULTS**

**Patients characteristics.** Of the 60 patients enrolled, 57 fulfilled the clinical and electrocardiographic inclusion criteria. Two patients treated with halofantrine and one patient treated with arteether were excluded because Holter recordings were not suitable for analysis. Clinical and biological findings are shown in Table 1. All patients presented typical clinical and biochemical signs of uncomplicated falciparum malaria. No significant difference was observed between patients with acute malaria and the control group regarding biometric parameters.

**QTc interval and QTc dispersion.** Mean ± SEM QTc interval and dispersion values calculated at 0, 9, and 24 hours in all treated patients are shown in Table 2. Patients treated with arteether or mefloquine showed no change in the QTc interval and QTc dispersion. Patients treated with quinine demonstrated a slight lengthening of the QTc interval and a moderate increase in QTc dispersion, with no value higher than 65 msec (P = 0.247; not significant). Patients treated with halofantrine showed high-grade QTc dispersion at 9 hours (P < 0.0001) and 24 hours (P < 0.01). Values higher than 100 msec were recorded in five patients in the halofantrine group (mean = 131 msec, range = 100–170 msec).

**Twenty-four–hour ECG recordings and QT dynamics.** Analysis of 24-hour ECG recordings showed no differences between patients treated with different antimalarial drugs (Table 2). Ventricular arrhythmia was not detected in any case. Ventricular extrasystoles (less than 500/day) were observed in patients treated with halofantrine or arteether but there were no statistical differences in comparison with the other groups.

The Q–Tc/RR regression slope data (mean ± SEM) obtained in the control and treatment groups are shown in Table 3. There was no significant difference between controls and patients treated with arteether or mefloquine. Patients treated with quinine decreased Q–Tc/RR slope in comparison with the controls and patients treated with arteether.
Patients treated with halofantrine showed higher mean Q-eT/RR regression slopes than controls and patients treated with any other drug \( (P < 0.0002) \). Scattergrams of the Q-eT-to-RR relationship in four patients treated with artemether, halofantrine, mefloquine, quinine, and one control are shown in Figure 1.

**Plasma concentrations.** Maximum plasma concentrations of quinine and mefloquine were observed 24 hours after drug intake (mean ± SEM: 4,022.1 ± 1,880.6 µg/L and 2,166.4 ± 883.3 µg/L, respectively; \( P < 0.001 \)). The plasma concentration of halofantrine was significantly increased nine hours after the first drug intake (955.1 ± 677.2 µg/L; \( P < 0.0001 \)). The maximum concentration of desbutyl-halofantrine was reached at 24 hours (111.12 ± 52.93 µg/L; \( P < 0.0001 \)). Artemether and DHA were not detectable in any case (Table 2).

The QTc interval, and QT dispersion at 9 and 24 hours were significantly correlated with plasma halofantrine concentration (\( P < 0.0001 \)), but not with plasma desbutyl-halofantrine concentration. Significant correlations with QTc interval and QT dispersion were also noted for quinine and mefloquine plasma concentrations (\( P < 0.0001 \)). The Q-eT regression slope was significantly correlated with the plasma level of halofantrine (\( P < 0.001 \)), but not with that of desbutyl-halofantrine. A significant correlation was also observed between the Q-eT regression slope and plasma drug concentration in patients treated with quinine (\( P < 0.006 \)).

**DISCUSSION**

The findings of this, albeit small, study provide a better understanding of the effects of the primary drugs used for treating chloroquine-resistant *P. falciparum* malaria on ventricular repolarization. Holter recordings showed no differ-

### Table 1

Clinical and biologic characteristics of patients and controls in the study*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mefloquine (n = 15)</th>
<th>Quinine (n = 14)</th>
<th>Halofantrine (n = 13)</th>
<th>Artemether (n = 15)</th>
<th>Controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27 ± 4.84</td>
<td>31 ± 13.1</td>
<td>29 ± 8.33</td>
<td>27 ± 5.4</td>
<td>31 ± 5.1</td>
</tr>
<tr>
<td>Men:women</td>
<td>150</td>
<td>140</td>
<td>11:2</td>
<td>8.7</td>
<td>96</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.3 ± 8.4</td>
<td>64.6 ± 14.1</td>
<td>68.6 ± 10</td>
<td>68.1 ± 8.3</td>
<td>66.6 ± 13.4</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>120 ± 22</td>
<td>118 ± 15</td>
<td>116 ± 15</td>
<td>120 ± 14</td>
<td>115 ± 15</td>
</tr>
<tr>
<td>Heart rate (per min)</td>
<td>75.8 ± 15</td>
<td>78.5 ± 12.3</td>
<td>82 ± 9</td>
<td>86 ± 14</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>Initial temperature (°C)</td>
<td>38.1 ± 1.2</td>
<td>37.9 ± 1.1</td>
<td>38 ± 1.3</td>
<td>38.3 ± 1.1</td>
<td>–</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.7 ± 4.1</td>
<td>12.5 ± 2.6</td>
<td>12.6 ± 2.7</td>
<td>14.2 ± 0.3</td>
<td>–</td>
</tr>
<tr>
<td>Platelets (10 kg/L)</td>
<td>240 ± 55</td>
<td>140 ± 62</td>
<td>130 ± 64</td>
<td>150 ± 10</td>
<td>–</td>
</tr>
<tr>
<td>Glycemia (mmol/L)</td>
<td>5.5 ± 0.6</td>
<td>6.0 ± 0.89</td>
<td>5.9 ± 1.2</td>
<td>6.2 ± 0.6</td>
<td>–</td>
</tr>
<tr>
<td>Potassium level (mmol/L)</td>
<td>3.8 ± 0.1</td>
<td>4.4 ± 0.2</td>
<td>4.6 ± 0.1</td>
<td>4.3 ± 0.5</td>
<td>–</td>
</tr>
<tr>
<td>Calcium level (mmol/L)</td>
<td>2.52 ± 0.06</td>
<td>2.39 ± 0.11</td>
<td>2.45 ± 0.04</td>
<td>2.55 ± 0.04</td>
<td>–</td>
</tr>
</tbody>
</table>

*Values are the mean ± SEM.

(P < 0.04). Patients treated with halofantrine showed higher mean Q-eT/RR regression slopes than controls and patients treated with any other drug (\( P < 0.0002 \)). Scattergrams of the Q-eT-to-RR relationship in four patients treated with artemether, halofantrine, mefloquine, quinine, and one control are shown in Figure 1.

**Plasma concentrations.** Maximum plasma concentrations of quinine and mefloquine were observed 24 hours after drug intake (mean ± SEM = 4,022.1 ± 1,880.6 µg/L and 2,166.4 ± 883.3 µg/L, respectively; \( P < 0.001 \)). The plasma concentration of halofantrine was significantly increased nine hours after the first drug intake (955.1 ± 677.2 µg/L; \( P < 0.0001 \)). The maximum concentration of desbutyl-halofantrine was reached at 24 hours (111.12 ± 52.93 µg/L; \( P < 0.0001 \)). Artemether and DHA were not detectable in any case (Table 2).

The QTc interval, and QT dispersion at 9 and 24 hours were significantly correlated with plasma halofantrine concentra-

### Table 2

Heart rate, QTc interval (min, max) QTc dispersion, and plasma drug concentration in patients treated for malaria*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mefloquine (n = 15)</th>
<th>Quinine (n = 14)</th>
<th>Halofantrine (n = 13)</th>
<th>Artemether (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (/min)</td>
<td>73.8 ± 15</td>
<td>78.5 ± 12.3</td>
<td>82 ± 9</td>
<td>86 ± 14</td>
</tr>
<tr>
<td>QTc min (msec)</td>
<td>368 ± 32.7</td>
<td>360.4 ± 27.6</td>
<td>369.2 ± 33</td>
<td>372.9 ± 29</td>
</tr>
<tr>
<td>QTc max (msec)</td>
<td>416.3 ± 33.3</td>
<td>413.5 ± 27.6</td>
<td>419.2 ± 30.5</td>
<td>419.5 ± 22.5</td>
</tr>
<tr>
<td>QTc dispersion (msec)</td>
<td>424.2 ± 26.6</td>
<td>441.2 ± 27.8</td>
<td>470.1 ± 44.1†</td>
<td>435.1 ± 24.2</td>
</tr>
<tr>
<td>Plasma drug level (µg/L)</td>
<td>422.6 ± 27.2</td>
<td>437.6 ± 30.4</td>
<td>479.5 ± 39.3‡</td>
<td>420.8 ± 29.0</td>
</tr>
<tr>
<td>H0</td>
<td>53.4 ± 14.5</td>
<td>53.1 ± 14.1</td>
<td>59.1 ± 14.9</td>
<td>47.2 ± 17.6</td>
</tr>
<tr>
<td>H9</td>
<td>47.6 ± 12.2</td>
<td>62.5 ± 23</td>
<td>83.2 ± 28‡</td>
<td>58.7 ± 16.5</td>
</tr>
<tr>
<td>H24</td>
<td>48.6 ± 13.1</td>
<td>64.7 ± 19.5</td>
<td>77.2 ± 33.7†</td>
<td>52.1 ± 13.0</td>
</tr>
</tbody>
</table>

*Values are the mean ± SEM. Values in parentheses are desbutylhalofantrine concentrations.

† \( P < 0.003 \).
‡ \( P < 0.001 \).
§ \( P < 0.01 \).

The findings of this, albeit small, study provide a better understanding of the effects of the primary drugs used for treating chloroquine-resistant *P. falciparum* malaria on ventricular repolarization. Holter recordings showed no differ-
ence between groups with regard to heart rate and incidence of arrhythmia episodes. The number of ventricular extrasystoles was higher in the halofantrine and artemether groups, but no repetition was recorded over a nychthemeral period.

Analysis of 12-lead ECGs in the halofantrine group demonstrated a significant increase in the QTc interval starting at nine hours and peaking at 24 hours. Changes in QTc values (pathologic cutoff greater than 440 msec) were significant at H9 and H24 (mean = 470 msec and 480 msec, respectively). These findings were in agreement with data reported in the literature and correlated with the plasma rate of halofantrine, but not with its desbutyl derivative. A significant increase in the QTc interval was not detected in patients treated with mefloquine or quinine. No significant change in the QT interval was observed in the group treated with artemether.

Our findings with artemether are of special interest because the effect of artemether on ventricular repolarization has not been extensively studied. In experimental studies involving acute administration of artemether at lethal doses in rats and dogs, Brewer and others observed cardiac toxicity and QT prolongation. Trials using clinically safe doses of artemether for the treatment of severe falciparum malaria have generally demonstrated no dysrhythmia or significant changes in ECG tracings. The major exception was a clinical study of 2,638 patients with uncomplicated falciparum malaria in which Ribeiro and Olliaro reported moderate lengthening of the QTc interval in 1.1% of the cases. However, that study failed to take into account the effects of hydration status and potential ionic disorders. A recent study showed no significant change in QTc interval when artemether was used in combination with lumefantrine, an antimalarial compound with some structural similarities to halofantrine. The possible effects of Plasmodium infection on cardiac repolarization have been raised by Seidlein and others among children and may explain why several cases of torsades de pointes and/or sudden death have been reported after treatment with halofantrine.

Study of the QT frequency-dependency revealed no modification of the circadian Q-eT/RR regression slope in patients treated with artemether or mefloquine. The lowest Q-eT/RR slope values occurred in patients treated with quinine and this difference was significant in comparison with the artemether and control groups. Using long-term Holter recordings to analyze rate-dependent QT interval changes, Locati and others demonstrated that quinidine-induced modifications of QT frequency-dependency were due to lowering of the QTc/RR regression slope during short cycles (unpublished data). In our study, Q-eT/RR regression slope values observed with quinine were close to those observed by Locati and others with quinidine. In patients treated with halofantrine, the QTc/RR regression slope was significantly higher than in other groups. This increase is a characteristic finding of Vaughan-Williams’ class III antiarrhythmic drugs. Okada and others demonstrated a significant increase in Q-eT/RR regression slope with various class III agents, including doxetilide and d-sotalol. Thus, as for class III agents, the mechanism underlying the effect of halofantrine on QT frequency-dependency probably involves a blockade of the HERG channel responsible for the rapid component of the delayed rectifier potassium channels (Ikr) rather than a quinidine-like effect. This conclusion is supported by the findings of Weisch and others, who demonstrated that halofantrine selectively blocked potassium channels Ikr in isolated feline ventricular myocytes.

The QTc interval, QT dispersion, and Q-eT regression slope were strongly correlated with the plasma concentrations of halofantrine, quinine, and mefloquine. No correlation was demonstrated in the artemether group because we were unable to detect the drug in the plasma in any patient studied. Artemether and DHA, which are known to cycle rapidly, have shorter half-lives that should have been detectable. The failure in the detection of the drug and its metabolite might be due to a problem with the assay or to an inappropriate sampling time.

This study includes several methodologic pitfalls. The first problem involves determination of the QTc interval and its dispersion. Although commonly used, Bazett’s formula overestimates or underestimates the QT interval in short or long cycles. In our study, this shortcoming probably had unavoidable consequences on dispersion measurement.

The second methodologic problem also involves circadian variations in dispersion. In a Holter study conducted with 17 healthy subjects, Ishida and others showed that dispersion was highest during the day (peak at approximately noon) and lowest in the evening (peak at approximately 6:00 PM). The obvious implication of this finding is that the autonomic nervous system plays a role; thus, the QT interval may vary depending on sympathetic tone. In this regard, it has been shown that the adrenergic tone predominates during the day and the QT interval is prolonged during sleep, regardless of the RR interval duration. It should also be noted that QT dispersion is not believed to depend on the heart rate in the same way as on the QT interval. In our study, the impact of circadian variations was minimized by computing only day time dispersion.

### Table 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Q-eT/RR slope*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether</td>
<td>14</td>
<td>0.170 ± 0.048</td>
</tr>
<tr>
<td>Quinine</td>
<td>15</td>
<td>0.135 ± 0.057</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>13</td>
<td>0.289 ± 0.118</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>15</td>
<td>0.145 ± 0.044</td>
</tr>
<tr>
<td>Controls</td>
<td>15</td>
<td>0.172 ± 0.039</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM.
† Quinine versus artemether and controls; P < 0.04.
‡ Halofantrine versus other antimalarial drugs; P < 0.0002.
FIGURE 1. Scattergrams of Q-eT plots against RR intervals. The horizontal axes represent the RR intervals (msec) and the vertical axes the QT intervals (msec). The Q-eT/RR slope is steeper with halofantrine (B) than with the control (E) and other antimalarial agents. During treatment with quinine (D), the rate dependency of the QT interval is lower, whereas, with artemether (A) and mefloquine (C), the rate dependency of the QT interval is similar in both groups.
Another methodologic problem involves the choice of technique to study QT dynamics. Several methods have been proposed to evaluate the QT/RR relationship. The first involves averaging every 30 seconds to analyze 2,880 QT intervals over a nyctohemeral period. This technique has been used to evaluate anti-arrhythmic drugs such as quinidine, d-sotalol, or verapamil, as well as over short periods of time before arrhythmia events occurred or during exercise tests. The second method involves selecting a QT with stabilized cardiac frequency to avoid the effect of lag hypertension. In our study, beat-to-beat measurements were averaged every 30 beats. This technique helped reduce lag hypertension effects and allowed reliable analysis of the relationship between QT and RR intervals.

Potential effects on ventricular repolarization must always be taken into account when selecting an agent for treatment of P. falciparum malaria. Based on the findings of this study, quinine, the first-line agent for severe or complicated malaria, is likely to induce moderate lengthening of the QTc interval and its dispersion. Results of our Q-T/RR regression slope study showed that quinine acts like a class Ia agent with a quinidine-like effect. Its effect on ventricular repolarization has no clinical incidence at the recommended dosage.

Our study provides further evidence that halofantrine is the most cardiotoxic of the most frequently used antimalarials. Its extensive effect on the QTc interval has been well documented and a few cases of severe ventricular arrhythmia or sudden death have been reported. The results of this study showed that halofantrine intake consistently led to an increase in QTc dispersion with values comparable to those observed in the long congenital QT syndrome in some cases. As previously observed, after myocardial infarction in patients prone to life-threatening arrhythmias, rate dependency of the QT interval is higher in patients treated with halofantrine. The mechanism underlying the effects of this drug on ventricular repolarization is similar to that of class III antiarrhythmic drugs such as d-sotalol. Consequently, halofantrine must be cautiously used especially for presumptive self-treatment. The QT changes must be taken into account when quinine and halofantrine are used in association with drugs likely to modify ionogram or block delayed rectifier potassium channels (e.g. diuretics, laxatives, and selective H1 receptor antagonists).

This study also indicates that mefloquine and artemether are free of any cardiotoxic effects when used at recommended safe clinical doses. However, it should be noted that mefloquine has well-documented neuropsychic effects and that artemether has been shown to be neurotoxic in experiments in rats.

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