Effect of artesunate and mefloquine in combination on the Fridericia corrected QT intervals in Plasmodium falciparum infected adults from Thailand

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Summary

OBJECTIVE To ascertain whether mefloquine (MQ) produces electrocardiogram (ECG) changes that could be a risk for Torsades de Pointe (TdP), a potentially malignant, ventricular tachyarrhythmia.

METHODS We measured the Fridericia corrected QT (QTcF) intervals on 12 lead ECGs on days (D) 0, 3, 7 in Plasmodium falciparum infected adults, treated with oral artesunate (AS) and MQ as a new fixed dose (n = 25) combination or loose tablets (n = 25) over 3 days. Target total doses were 12 mg/kg of AS and 24–25 mg/kg of MQ. MQ concentrations ([MQ]) were measured by HPLC.

RESULTS All ECG intervals were similar between drug arms and were combined for analysis. Mean QTcF values were 389 (D0), 407 (D3) and 399 (D7) ms (Ps < 0.003 vs. D0); corresponding heart rates and [MQ]s were 83, 67 and 73 beats/minute (Ps £ 0.0003 vs. D0) and 0, 3095 and 1721 ng/ml. One male patient (loose arm) had a D3 QTcF 504 ms (D0 406 ms, D7 433 ms). In the modelling of QTcF and JTcF from D0 to D7, significant effects were observed individually for [MQ], temperature and heart rate (HR). The MQ AUC0–¥ was not a significant factor. Using a manual descending, model building approach to select variables, the HR was the only significant variable (P = 0.001) over time in the model that best explained the changes in the QTcF and JTcF intervals.

CONCLUSIONS In this small group of patients, slowing heart rates due to malaria resolution best explained the observed increases in the QTcF intervals.

KEYWORDS Electrocardiogram, QT interval, Torsades de Pointe, mefloquine, artesunate, malaria

Introduction

Drug regulatory authorities demand the assessment of drugs for their potential to cause Torsades de Pointe (TdP), a broad complex, ventricular tachycardia that may lead to ventricular fibrillation and sudden death (Dessertenne 1966). Measuring the corrected QT (QTc) interval on an electrocardiogram (ECG) is recommended but several factors affect its length, including gender, diurnal variation, eating food, body temperature, heart rate (HR), hypokalaemia and hypocalcaemia (White 2007). The risk of TdP and QTc prolongation is not linear and there are many QT correction formulae to choose from (Yap & Camm 2003), including a new QT correction formula derived from malaria patients (Price et al. 1998). QT dispersion, advocated previously, is a poor risk marker (Batchvarov & Malik 2000). Seldom mentioned is the JT interval, the ECG measurement of ventricular repolarisation. The regulatory guidelines [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH guidelines)] acknowledge such challenges and recommend using the Bazett (QTcB) and Fridericia (QTcF) corrected QT data (http://www.ich.org, accessed November 2009).

Ventricular repolarisation is mediated mainly by the outward flow of potassium (K+) ions from myocytes...
through the slow ($I_{K_s}$) and rapid ($I_{K_r}$) components of the delayed rectifier $K^+$ channel. Inhibiting $K^+$ outflow leads to heterogeneous repolarisation, an environment favouring the development of TdP. The $I_{Kr}$ channel, encoded by the human ether a go go (hERG) gene on chromosome 7, is the target of a broad range of drugs with different chemical structures e.g. halofantrine, cisapride, erythromycin, chlorpromazine, astemizole and quinidine (Curran et al. 1995; Sanguinetti et al. 1995).

Halofantrine, a potent $I_{Kr}$ inhibitor, causes a dose dependent QTc interval increase and ventricular fibrillation in malaria patients; a problem that was detected only after registration (Monlun et al. 1995; Touze et al. 1996; Gundersen et al. 1997; Malvy et al. 2000; Mbai et al. 2002). Increases in the mean QTc intervals (up to 20 ms) have been observed in recovering malaria patients with oral arteunate (AS), amodiaquine, sulphadoxine/pyrimethamine (S/P), and dihydroartemisinin/piperine on around day (D) 3 when patients are afibrile and have reduced heart rates (Ribeiro & Olliaro 1998; Ngouesse et al. 2001; Mytton et al. 2007). By contrast, one study found a decrease in the mean D3 QTc interval and mean D3 HR in patients treated with atovaquone proguanil alone or combined with oral AS (Gupta et al. 2005).

Mefloquine (MQ) has a good cardiac record (ter Kuile et al. 1995; Jaspers et al. 1996). Case reports (Fonteyne et al. 1996; Richter et al. 1997) documented atrial flutter with 1 to 1 conduction (treatment), and atroventricular conduction through an aberrant pathway (prophylaxis). Asymptomatic sinus bradycardia has been reported but at similar rates (18–36%) to CQ and S/P, suggesting malaria resolution as the cause (Kofi Ekue et al. 1983; Ekue et al. 1987). First degree heart block, sinus arrhythmia, non specific T wave changes and prolonged QTc intervals have also been observed in MQ treatment studies but detailed data are lacking (Harinasuta et al. 1987; Laothavorn et al. 1992). One treatment study documented a positive correlation between plasma MQ concentrations and the QTcB but all QTcB intervals were within normal limits (Touze et al. 2002). MQ does not produce significant QTc interactions when given with quinine or arteether/lumefantrine and MQ concentrations did not correlate with the QTc intervals (Supananarond et al. 1997; Na-Bangchang et al. 1999; Bindschedler et al. 2000). However, the risk of QTc prolongation increased when MQ treatment failures were treated with halofantrine (Nosten et al. 1993). MQ preferentially inhibits the $I_{Kr}$ channel, which may explain the synergistic QTc prolonging effect of MQ and halofantrine (Kang et al. 2001). There are few data on the effect of AS on the ECG intervals, one key study of intravenous (IV) AS in 21 severe malaria patients found no effect on the PR, QRS, QTcB and JTcB intervals (Maude et al. 2009).

Because many factors affect the QTc interval, obtaining pharmacokinetic (PK) data is crucial for interpreting QTc data. We report the effects on the ECG intervals in *Plasmodium falciparum* infected adults treated with AS and MQ.

**Methods**

Conduct of clinical trial

This randomised, safety and PK study of adults (weight >39 kg, no study drug allergies) with acute uncomplicated *P. falciparum* compared a new, fixed dose combination of AS and MQ to non fixed AS + MQ, the current standard in Thailand. A sample size of 25 patients per drug arm was deemed adequate for intense PK sampling. The study was conducted at the Hospital for Tropical Diseases, Bangkok, Thailand, from December 2004 to July 2005. It was approved by the ethical committees of the Faculty of Tropical Medicine, Mahidol University, and of the WHO. The trial is registered (http://www.controlled-trials.com/mrc/trial/228997/DNDi).

Drugs were administered as follows: (i) two fixed dose, AS/MQ (Farmanguinhos, Brazil) tablets (one tablet = 100 mg AS, 200 mg MQ), daily for 3 days, (ii) AS [Arsumax® (50 mg of AS) Sanofi-Aventis, France] 4 mg/kg (D0), AS4 mg/kg + MQ15 mg/kg (D1), AS4 mg/kg + MQ10 mg/kg (D2); MQ = 250 mg MQ base (Roche, Basel, Switzerland). Patients were hospitalised for 28 days. Vital signs were monitored 4–6 hourly up until D21; thereafter daily. PK samples were taken at baseline, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and D1, 2, 3, 7, 14, 21, 28. The plasma was stored in cryotubes at −70 °C and sent to the Universiti Sains Malaysia for PK analysis (data to be presented elsewhere).

**ECG methods**

Standard, 12-lead ECGs (50 m/s, voltage sensitivity = 1 mV/cm) were done after patients lay rested for about 5 min at baseline, D3, 7 and 28 (if D7 ECG was abnormal). Day 3 (72 h) approximates the time of maximum MQ concentrations of the standard AS+MQ regimen (Price et al. 1999) and of the fixed dose AS/MQ used in this study (Krudsood et al. 2010) but was some 12 h after the mean Tmax when MQ was given as 8 mg/kg/day × 3 days (Ashley et al. 2006). ECGs were scanned, digitised and converted into an ECG Scan Extensible Mark-up Language (XML) format so ECG intervals (Lead II) could...
be measured with on screen digital callipers. The first
deflection of the QRS complex and the intersection of the
descending part of the T wave (positive T wave) with the
isoelectric line defined the start and end of the QT interval,
respectively. If the U wave interrupted the T wave before it
returned to baseline, the QT interval was measured as the
nadir between T and U waves. If it was not clear whether a
second deflection of the T wave was a U wave, it was
included in the QT interval. All ECGs were reviewed by a
cardiologist and all abnormal ECGs were reviewed again
by a senior cardiologist.

The QTc intervals were calculated using three formulae:
(i) Bazett’s – QTcB = QT/(RR)0.5, (ii) Fridericia –
QTcF = QT/(RR)0.33, and (iii) the new malaria formula
(Price et al. 1998), QTcn = QT/(RR)0.4. The JTc was
derived from the QTc QRS difference, using an upper limit
of normal (ULN) of 110 ms for the QRS interval. Because
the Fridericia formula gave the best fit (regression line)
between all the QT and RR intervals, the QTcF and JTcF
were chosen as the primary intervals. All analyses were two
sided and a P value of ≤ 0.05 was considered significant.
No adjustment was made for multiple comparisons.

Statistical methods

Continuous data were analysed using the paired/unpaired
$t$-tests (normal data) or sign rank/Mann–Whitney $U$-tests
(skewed data), as appropriate.

Categorical analyses of outlying QTc values (following
ICH guidelines) were performed to ascertain the propor-
tions of patients who had: (i) absolute QTcF interval
increases ≥ 30 ms and ≥ 60 ms over baseline, (ii) QTcF
increase ≥ 25% compared to baseline [33], (iii) QTcF
interval ≥ 500 ms (iv) females with at least one QTcF ≥
450 ms, and (v) males with at least one QTcF ≥ 430 ms.

A linear mixed effects model explored over time (D0, D3
and D7) the relationships between the QTcF and JTcF
intervals and age, sex, treatment, temperature, MQ con-
centrations and HR. The model initially estimated times of
measurements alone (i.e. no independent variables were
used) to test for a linear trend in time and a random
intercept for an initial effect (i.e. an effect without the
influence of the independent variables). The random slope
in time was then further tested for an increase over time of
the QTcF and JTcF intervals. The random slope allows the
calculation of an overall slope (coefficient) for the param-
eter being tested and the difference from this mean to be
calculated for each subject. The times of measurements
were excluded in the models when temperature, HR and
MQ concentrations were assessed because time is already
accounted for in these repeated factors. The random slope
was not included in these models because the estimated
variance-covariance matrix specified for the random
intercept and the random slope were not positive. There-
fore, estimating the correlation between the random
coefficients could not be performed.

The clinical and ECG data were managed and analysed
by a clinical research organisation, following an analysis
plan with supplementary ECG and ECG PK analyses (WT,
MV). Data were entered in Clinitrail v4.3 database (Phase
Forward, Waltham, Massachusetts, USA) and analysed
with SAS® version 8 (SAS Institute, Cary, NC, USA) and
SAS® version 9.3.1 (2nd analyses). Further analyses (simple
correlations, ANOVA, ANCOVA and logistic regression) are
presented in Appendix S1.

Results

Descriptive analyses

Twenty five patients per drug arm were enrolled (Table 1).  Most patients were male.  Two patients developed early
treatment failure and were withdrawn from the study on
rescue treatment. 145 ECGs were analysed (D0 = 50,
D3 = 47, D7 = 48). Because the ECG interval and HR data
were very similar between the fixed and non fixed arms
(data not shown), it was decided post hoc to combine the
data. Serum potassium data were available mostly for D0
only. The mean and range values were very similar between
the fixed and loose groups: 3.6 (2.8–4.4) vs. 3.7 (2.7–6.7)
mmol/l.

The mean PR intervals changed little over time (Table 2).
There was a trend towards a higher median D3 QRS
interval vs. baseline. The significant changes over time were

<table>
<thead>
<tr>
<th>Variable</th>
<th>AS/MQ fixed N = 25</th>
<th>AS+MQ loose N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>26.6 (17–50)</td>
<td>28.9 (16–45)</td>
</tr>
<tr>
<td>Mean weight in kg (range)</td>
<td>50.1 (6.26)</td>
<td>51.0 (6.36)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>19 (76)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Temperature (°C)*</td>
<td>38.5 (37.3–40)</td>
<td>38.2 (37–40)</td>
</tr>
<tr>
<td>Asexual parasitaemia (/μl)*</td>
<td>(69–170 800)</td>
<td>(20–140 280)</td>
</tr>
<tr>
<td>FCT (days)*</td>
<td>2.3 (1–7)†</td>
<td>2.3 (1–3)</td>
</tr>
<tr>
<td>PCT (days)*</td>
<td>1.89 (1–3.5)†</td>
<td>1.66 (0.5–3) days</td>
</tr>
<tr>
<td>$T_{max}$ (h)‡</td>
<td>72 (19.1)</td>
<td>70.9 (13.5)</td>
</tr>
<tr>
<td>MQ $C_{max}$ (ng/ml)‡</td>
<td>3279 (1252)</td>
<td>3239 (734)</td>
</tr>
</tbody>
</table>

*Mean (range).  †Based on 23 patients.  ‡Mean (standard deviation).
Table 2 Summary of the ECG intervals, the temperature and heart rate data in patients who were treated with either the fixed or loose dose combinations of artesunate and mefloquine. Data are shown as mean (ranges) and compared by the paired t-test, except where indicated. Summary data are for all subjects on that day (D0 = 50, D3 = 47, D7 = 48); differences between Days are based on paired comparisons.

<table>
<thead>
<tr>
<th>Day</th>
<th>Temperature (°C)</th>
<th>Heart rate/min</th>
<th>PR (ms)</th>
<th>QRS (ms)</th>
<th>QT (ms)</th>
<th>JT (ms)</th>
<th>JTcF (ms)</th>
<th>JTcn (ms)</th>
<th>QTcF (ms)</th>
<th>QTcB (ms)</th>
<th>JTcB (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3–D0</td>
<td>-1.2 (-3 to 0.5)</td>
<td>-15 (-43 to 20)</td>
<td>0 (-61 to 36)</td>
<td>42 (-55 to 128)</td>
<td>18 (-29 to 98)</td>
<td>21 (-31 to 97)</td>
<td>13 (-36 to 97)</td>
<td>18 (-29 to 96)</td>
<td>12 (-51 to 96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
<td>0.97</td>
<td>0.055</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D7–D0</td>
<td>-1.2 (-3 to 1.3)</td>
<td>-40 (-28 to 20)</td>
<td>-3 (-99 to 30)</td>
<td>23 (-70 to 132)</td>
<td>-22 (-61 to 135)</td>
<td>13 (-27 to 110)</td>
<td>11 (-23 to 104)</td>
<td>8 (-32 to 68)</td>
<td>8 (-25 to 94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.000</td>
<td>0.0003</td>
<td>0.23</td>
<td>0.67</td>
<td>0.0001</td>
<td>0.0006</td>
<td>0.01</td>
<td>0.28</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Median (range), QRS was not normally distributed. QRS comparisons used the Sign test.

in the mean HR, the mean QT/QTc and JT/JTc values (Table 2 and Figure 1). Seven of 47 (14.9%) patients developed sinus bradycardia (<60/min) on their D3 ECGS, which was still present in 2 of 48 (4.16%) patients on the D7 ECG. Pulse rate ranges for the latter two patients were:

- (i) 60–76, 66–78 on D3,
- (ii) 68–80, 76–80 on D7,
- (iii) 66–80, 76–84 on D8, and
- (iv) 66–84, 72–84 on D9.

Mean D3 mefloquine concentrations ([MQ])s were similar (P = 0.42) between patients with (2789 ng/ml) and without (3156 ng/ml) sinus bradycardia. No patients had sinus arrhythmia. Two patients developed transient non specific T wave changes.

No MQ was detected on D0. [MQ]s on D3 and D7 ranged (mean) from 1346 to 5796 (3095) and 600 to 2917 (1721) ng/ml, respectively, and were similar between the fixed and non fixed arms on D3 (3013 vs. 3165 ng/ml, P = 0.65) and D7 (1577 vs. 1846 ng/ml, P = 0.16).

Categorical analyses of outlying QTcF values

In total, 10 fixed and 11 non fixed patients had 33 ICH defined alert values, including 3 QTcF values at baseline. Fourteen and 7 patients had increases in the QTcF ≥30 ms on D3 and D7, respectively, and 3 (D3 = 2) patients had QTcF increases ≥60 ms. Eleven of the 14 and 4 of the 7 patients had QTcF values within the normal range for their sex (Table 3). One male (loose arm) patient had a QTcF increase of 4.61 ms at D3 (72 h) and 10.75 ms at D7; corresponding changes in heart rates were small: 63, 61, 70 beats/min. Another male (fixed arm) patient had a QTcF increase of 26.6% over baseline: 346, 430, 438 ms with large declines in heart rates: 102, 65, 67 beats/min.

Linear mixed effects model

The means of the random intercept estimates (i.e. the effect of QTcF or JTcF without the influence of any factors/ independent variables) were 393.42 ms for the QTcF and 292.69 ms for the JTcF (Table 4). The increase in time (random slope) was 0.06401 ms per hour (QTcF) for an increase of 4.61 ms at D3 (72 h) and 10.75 ms at D7; for the JTcF, the increase was 0.07945 ms/h: 5.72 ms (D3) and 13.35 ms (D7). No significant effects were seen for the covariates drug formulation, age and sex.

Significant effects were observed in the modelling of QTcF and JTcF with [MQ], but not the MQ AUC values, temperature and HR. Increasing blood MQ concentrations at each time of measurement led to a mean increase of 17.96 ms (QTcF) and 19.52 ms (JTcF) at D3, and 9.40 and
10.21 ms at D7, respectively. An increase in [MQ] of 1 ng/ml lead to an increase of 0.006 ms in the QTcF as well as the JTcF intervals.

A mixed model was run to estimate the mean changes in [MQ] between D0-D3 and D0-D7; the mean differences were 856 ng/ml and 642 ng/ml, respectively. Allowing for the modelling of 2 slopes for the same periods, the model found a mean increase of 0.34 in QTcF and 0.37 ms in JTcF, respectively, between D0 and D3, and a mean decrease of 0.08 ms in QTcF and JTcF between D3 and D7.

By contrast, increasing values of temperature and HR decreased the QTcF and JTcF values (Table 4). An increase in temperature of 1°C led to a decrease in QTcF of 7.99 ms and JTcF of 10.25 ms. An increase of 1 beat/min in the HR led to a decrease of 0.8 ms in QTcF and 1.1 ms in JTcF.

Using a manual descending, model building approach of all fixed (treatment arm, sex and age) and random (MQ concentrations, temperature and HR) variables, the HR was the only significant variable (P = 0.001) over time in the model that best explained the changes in the QTcF and JTcF intervals.

### Discussion

This study has shown that the mean QTcF and JTcF intervals rose initially then fell during treatment of drug resistant *P. falciparum*. Our analyses found consistently that these observations were related significantly and inversely to changes in the HR which slowed as malaria resolved.

Our data have implications for other antimalarial drugs because disease resolution will always explain part of the increase in the QTc interval and, possibly, the further slowing of the HR because ECGs are done after a short resting period. However, there are three caveats for practising clinicians. It is important to use therapeutic doses, be wary of co-prescribing AS/MQ with drugs that could prolong the QTc interval (e.g. antiepileptics, AS/MQ should never be used for treating halofantrine failures), and to not disregard cardiac symptoms. There is a move towards age based dosing of antimalarial drugs in some malaria endemic countries; therefore, some patients will receive doses above the therapeutic range which could adversely affect tolerability (Taylor et al. 2006).

### Table 3 Patients with ICH alert values* of the absolute QTcF intervals and their changes from baseline

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 3</th>
<th>Δ D3–0</th>
<th>Δ D3–0%</th>
<th>Day 7</th>
<th>Δ D7–0</th>
<th>Δ D7–0%</th>
<th>HR D0</th>
<th>HR D3</th>
<th>HR D7</th>
<th>D3 [MQ]</th>
<th>D7 [MQ]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>387</td>
<td>417</td>
<td>30</td>
<td>7.8</td>
<td>387</td>
<td>0</td>
<td>0.0</td>
<td>90</td>
<td>68</td>
<td>72</td>
<td>2542</td>
</tr>
<tr>
<td>2</td>
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<td>396</td>
<td>444</td>
<td>48</td>
<td>12.1</td>
<td>412</td>
<td>16</td>
<td>4.0</td>
<td>91</td>
<td>67</td>
<td>71</td>
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<td>6.6</td>
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*ICH alert values are:
(i) post baseline QTcF increases ≥ 30–<60 ms and ≥ 60 ms.
(ii) post baseline QTcF values of ≥ 430–<450 ms & ≥ 450 ms (males).
(iii) post baseline QTcF values of ≥ 450–<470 ms & ≥ 470 ms (females).
(iv) post baseline QTcF values ≥ 500 ms.
Effect of AS and MQ in combination on the QTcF intervals

| Effect | Estimate | Standard error | df  | t value | P > |t| |
|--------|----------|----------------|-----|---------|-----|---------|
| QTcF = f([t]) | 393.31 | 3.6865 | 46 | 106.69 | <.0001 |
| TIME_in_hrs | 0.06401 | 0.02354 | 42 | 2.72 | 0.0095 |
| QTcF = f([MQ]) | 389.89 | 2.7191 | 42 | 143.39 | <.0001 |
| MQ_conc | 0.005958 | 0.0018 | 42 | 3.31 | 0.0019 |
| QTcF = f([T°C]) | 699.13 | 75.323 | 49 | 9.28 | <.0001 |
| VSTEMP | −7.9988 | 2.0026 | 47 | −3.99 | 0.0002 |
| QTcF = f([HR]) | 457.49 | 10.1013 | 49 | 45.29 | <.0001 |
| ECGHR | −0.7891 | 0.1289 | 47 | −6.12 | <.0001 |
| JTcF = f([t]) | 292.6 | 3.5372 | 46 | 82.72 | <.0001 |
| TIME_in_hrs | 0.07945 | 0.02668 | 42 | 2.98 | 0.0048 |
| JTcF = f([MQ]) | 289.71 | 3.3848 | 42 | 85.59 | <.0001 |
| MQ_conc | 0.006476 | 0.001369 | 42 | 4.13 | 0.0002 |
| JTcF = f([T°C]) | 684.76 | 84.0703 | 49 | 8.15 | <.0001 |
| VSTEMP | −10.2509 | 2.2351 | 47 | −4.59 | <.0001 |
| JTcF = f([HR]) | 379.98 | 10.3313 | 49 | 36.78 | <.0001 |
| ECGHR | −1.0769 | 0.1322 | 47 | −8.14 | <.0001 |

| MQ_conc | 0.005958 | 0.0018 | 42 | 3.31 | 0.0019 |
| VSTEMP | −7.9988 | 2.0026 | 47 | −3.99 | 0.0002 |
| QTcF = f([HR]) | 457.49 | 10.1013 | 49 | 45.29 | <.0001 |
| ECGHR | −0.7891 | 0.1289 | 47 | −6.12 | <.0001 |
| JTcF = f([t]) | 292.6 | 3.5372 | 46 | 82.72 | <.0001 |
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| VSTEMP | −10.2509 | 2.2351 | 47 | −4.59 | <.0001 |
| JTcF = f([HR]) | 379.98 | 10.3313 | 49 | 36.78 | <.0001 |
| ECGHR | −1.0769 | 0.1322 | 47 | −8.14 | <.0001 |

There are few PK ECG data on MQ in patients. Touze et al. (2002) found no significant changes in the QTcB interval or QTcB dispersion in 15 MQ treated, falciparum infected patients but, by simple regression, plasma MQ concentrations correlated positively with both variables. Our model found also a positive relationship between the QTcF and JTcF and MQ concentration with a mean increase of 0.34 in QTcF and 0.37 ms in JTcF by D3 followed by a mean decrease by D7 of 0.08 ms for both the QTcF and JTcF. This relationship disappeared when all factors were included in the model to adjust for their effects on each other and the HR remained the only significant factor for the change in the QTcF and JTcF. These findings suggest a neutral effect of MQ concentrations arising from therapeutic dosing on the QTcF and JTcF intervals but do not exclude the possibility of a weak positive relationship.

A low (approximately 15%) proportion of our patients developed new sinus bradycardia on D3 that was independent of D3 MQ concentrations and resolved mostly by D7, similar to the findings of others (Ekue et al. 1987). Interestingly, the pulse rates of the two ECG bradycardic patients did not show bradycardia, suggesting the short rest before the ECG was an important contributory factor. Malaria itself may have a small effect on the ECG intervals.

von Seidlein et al. (1997) found a weak positive correlation between the D0 parasitaemia and the QTcB interval in falciparum infected children, whereas we found no correlations between D0 parasitaemia and temperature and PR, QRS, QTcF and JTcF intervals. More data are needed to assess the possible malaria effects on the ECG.

The ICH guidelines recommend the Bazett and Fridericia correction formulae for ECG studies and focus on healthy volunteer studies in Western populations where ischaemic heart disease is prevalent. Using either formula in placebo controlled studies, a net mean increase in QTc interval of ‘around’ 5 ms (upper 95% CI of 10 ms) is a ‘concerning level’ and an absolute increase to >500 ms is of ‘particular concern.’ We chose the Fridericia correction formula based on the best fit of all of the QT HR data and explored the JTc and JTc intervals which are not in the ICH guidelines.

One patient had a D3 QTcF exceeding 500 ms without a substantial fall in his HR. His D3 [MQ] was below the sample mean so this increase might be explained partly by MQ acting on ‘sensitive’ Kᵢ₅ channels. Another patient had a percentage increase over baseline exceeding the 25% threshold used by some malariologists (Nosten et al. 1993) but he had marked falls in his HR. Several patients had QTcF increases of 230 and 260 ms over baseline but most had QTcF values in the normal range. The mean D3 D0 change in the QTcF was 18 ms (upper 95% CI of 26 ms) which was higher than the QTcn values of 13 and 21 ms, respectively. Of note is that the least accurate correction formula, Bazett, had the least mean QTcB increase of 5 ms with an upper 95% CI of 12 ms. These differing mean changes highlight the variation in results obtained by using different formulae and leave the question open as to which formula is optimal. The mean QTcF and QTcn increases over baseline were higher than the concerning values of the ICH guidelines and suggests that the ICH limits may not be applicable to febrile patients. We also explored the use of the JTc interval and defined a clinically significant value as any value exceeding the ULN because an increase in ventricular repolarisation is important for developing TdP. However, there are no regulatory guidelines defining the JTc limits of concern. More research is needed to define these and to compare the usefulness of the JTc vs. the QTc intervals.

Our study had limitations. The sample size was small and recruited predominantly fit young men. This limits the applicability of our findings to populations where ischaemic heart disease is rare. Only three ECGs per patient were performed. Performing several ECGs at each time point to reduce the intra individual variation would have been more informative.
which would have yielded more data. We did not measure
the red cell transketolase (for thiamine deficiency), serum
calcium and magnesium and only measured the serum
potassium at baseline. There were multiple analyses and
some statistically significant results may have occurred by
chance.

To conclude, the mean QTc interval increase was
consistently and independently related to the fall in HR.
Although the mixed effects model suggested a possible
weak positive relationship with MQ concentrations, this is
of limited clinical significance at therapeutic doses.

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employee. The views expressed in this paper are those of
the co-authors and not those of the WHO or the CRP-
Santé. We dedicate this work and publication to the late
Professor S. Looareesuwan. He was a well liked colleague
who played a significant part in the AS-MQ development
project.

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Supporting Information

Additional Supporting Information may be found in the online version of this article: Appendix S1. Correlations

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