NO EVIDENCE OF CARDIOTOXICITY DURING ANTIMALARIAL TREATMENT WITH ARTEMETHER-LUMEFANTRINE

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Abstract. Artemether-lumefantrine is a new fixed antimalarial combination effective against multidrug-resistant falciparum malaria. A prospective electrocardiographic study was conducted in 150 patients receiving artemether-lumefantrine and 50 treated with artesunate-mefloquine. There was no evidence for clinically significant changes in the electrocardiographic intervals and in particular no relationship between plasma concentrations of lumefantrine and QTc prolongation. Artemether-lumefantrine does not have significant cardiac effects at therapeutic doses.

Artemether and lumefantrine (benflumetol) is a new combination effective against multidrug-resistant falciparum malaria. Lumefantrine is a racemic fluorene derivative with the chemical name 2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]-ethanol. It conforms structurally, to the ary1-amino alcohol group of antimalarials including quinine, mefloquine, and halofantrine. Other antimalarials notably quinine, and to a greater extent quinidine and halofantrine, are known to prolong ventricular repolarization reflected in prolongation of the electrocardiographic QTc-interval at therapeutic dosages, and halofantrine has been associated with sudden death. Artemether is a methyl-ether derivative of dihydroartemisinin, derived from artemisinin (Qinghaosu). Artemether, and the closely related compound arteether, given in high doses by intramuscular injection prolong the QTc-interval in rats and dogs, which has given rise to concern that similar effects could occur in clinical use. However, there is no evidence from large prospective clinical studies of any cardiotoxicity with this compound in humans. Artemether-lumefantrine has usually been given in a 4-dose regimen comprising a total of 320 mg of artemether and 1,920 mg of lumefantrine for adults. In Thailand, 2 studies were conducted with a 6-dose regimen that gave higher cure rates than the 4-dose regimen and was equally well tolerated. These large dose-optimizing studies with higher dose regimens provided the opportunity to conduct detailed electrocardiographic studies and to relate any changes observed to the plasma concentrations of lumefantrine.

METHODS

Electrocardiographic monitoring and measurement of plasma lumefantrine concentrations were conducted in a randomized, 2-center trial conducted in adults and children more than 2 years old presenting with uncomplicated falciparum malaria in Bangkok, involving predominantly Thai and Mon subjects, or in a camp for displaced persons (predominantly Karen) living on the western border of Thailand. After giving informed consent, patients were allocated randomly to receive either artemether-lumefantrine, adult dose: 4 tablets twice a day for 3 days (each tablet contains 20 mg of artemether and 120 mg of lumefantrine) or the current standard combination treatment: artesunate in a single daily dose of 4 mg/kg/day for 3 days plus mefloquine in a split dose, i.e., 15 mg/kg on day 2 and 10 mg/kg on day 3. Blood microscopy was performed daily until 2 negative results were obtained, then weekly. Axillary temperature was measured daily until day 3. These studies were approved by the Ethical Committee of the Faculty of Tropical Medicine, Mahidol University, and the Karen Refugee Committee.

Five venous blood samples were withdrawn from all patients treated with artemether-lumefantrine. To optimize information, sampling times were chosen according to 1 of 2 randomized schedules: before dose 2 (or 3), before dose 4 (or 5), before dose 6, 8–16 hours after dose 6, and at day 7 (the schedules were only different for the first 2 sampling times). At each time point 4 ml of blood was collected into heparinized tubes and centrifuged at 1,000 rpm for 15 min before freezing at −70°C. Plasma concentrations of lumefantrine were measured using high-performance liquid chromatography with UV detection. The limit of quantitation was set to 100 ng/ml (interassay coefficient of variation <10%).

Electrocardiograms (ECGs). Electrocardiographic monitoring (Autocardiner FCP-2155; Fukuda Denshi Co., Ltd., Tokyo Japan) was performed at baseline, day 7, and day 28 for all patients. In the group treated with artemether-lumefantrine, an additional 4 ECGs were performed within the first week at the same time as blood sampling for antimalarial drug levels. For patients receiving artesunate-mefloquine, an additional 3 ECGs were taken about 1 hr after the first and second dose of mefloquine, respectively, on day 1 and day 2, and again about 24 hr after the second dose of mefloquine.

Electrocardiographic intervals were measured automatically by the machine and their absolute and percentage changes from baseline were summarized. The QT interval and heart rate were used to calculate the QTc interval using Bazett’s formula: QTc = QT/√(RR).

The QTc interval as the response variable was compared between treatments. Times of ECG recordings were similar but not identical for all subjects; thus, they were classified as ECG numbers 1 to 6 (days 0 [after baseline], 1, 2, 3, 7, and 28). A statistical model was fitted including QTc values at baseline (day 0), age, heart rate, center, and ECG number as secondary covariates and treatment as the main effect. To account for the grouping of QTc values within an individual, patient effect was added to the model as a random effect. Changes in mean estimates of QTc at different time points
were considered in reference to the mean estimate of day 28 (ECG number 6), when malaria effects were expected to have disappeared. Within the group treated with artemether-lumefantrine, a similar model was fitted except that the plasma lumefantrine concentration was used as the main effect. No plasma samples were taken at day 28. There have been extensive recent studies of the pharmacokinetic properties of lumefantrine and mefloquine. Lu-

Full clinical details of this study will be reported elsewhere. None of the patients had a history of arrhythmias or syncopal episodes. Clinical baseline characteristics were similar in both groups (Table 1). The median (range) age and body weight were 22 years (2–63) and 50 kg (8–81), respectively. There were no significant adverse cardiovascular episodes.

Electrocardiographic findings. Electrocardiographic data were available for 199 patients, (150 treated with artemether-lumefantrine and 49 treated with artesunate-mefloquine) including 34 children ≤12 years old. The median (range) heart rate at baseline was 89 (54–162) bpm. This decreased during the course of the treatment. The median (range) baseline PR interval was 138 (99–247) msec and the median (range) QRS interval was 92 (30–116) msec. Both remained unchanged following treatment. At baseline, the median (range) QTc was 412 ms (354–484). Excluding baseline measurements, 1,085 QTc machine-read measurements were available, 859 from patients treated with artemether-lumefantrine and 226 from patients treated with artesunate-mefloquine. A total of 711 observations were available for the evaluation of the effect of the plasma lumefantrine concentration on QTc interval, in which there were detectable plasma lumefantrine concentrations. The day 28 intervals were considered to represent the normal values for the individual since plasma lumefantrine concentrations are below the level of detection (<50 ng/ml) by this time; setting these values to zero drug effect resulted in an additional 128 observations; a total of 839 observations for lumefantrine.

There was no significant difference in pretreatment QTc values between the 2 drug groups. Fitting the mixed effect model, QTc at baseline, age, heart rate, center, and ECG number were each found to have statistically significant effects on the QTc interval. There was no evidence of a treatment effect on the QTc interval (Table 2). The greatest increase in QTc during treatment, compared with day 28, was estimated to be 8 msec ($P < 0.0001$) at the fourth ECG, approximately 67 hr after the start of the treatment. To ex-

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Multivariate analysis of the factors affecting the electrocardiographic QTc interval</th>
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<tbody>
<tr>
<td>Effect</td>
<td>Estimate (msec)</td>
</tr>
<tr>
<td>Baseline QTc</td>
<td>0.56*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.26*</td>
</tr>
<tr>
<td>Heart rate (f/min)</td>
<td>0.3*</td>
</tr>
<tr>
<td>Center</td>
<td>−8.7†</td>
</tr>
<tr>
<td>ECG number</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−5.3‡</td>
</tr>
<tr>
<td>2</td>
<td>−0.60‡</td>
</tr>
<tr>
<td>3</td>
<td>4.5‡</td>
</tr>
<tr>
<td>4</td>
<td>8.07‡</td>
</tr>
<tr>
<td>5</td>
<td>4.03‡</td>
</tr>
<tr>
<td>6</td>
<td>421§</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* Estimated effect in msec for every unit increase.
† Estimated effect of center (Bangkok versus Mae La) on QTc (msec).
‡ Estimated mean difference in QTc (msec) using electrocardiogram (ECG) number 6 (day 28) as a normal reference.
§ Estimated mean QTc (msec) at ECG number 6 (day 28).
There has been natural concern over the cardiotoxic potential of newly introduced antimalarial drugs since the unexpected discovery of the marked effects of halofantrine on ventricular repolarization, well after it had been introduced in clinical practice. \(^2\),\(^3\),\(^13\),\(^14\) Electrocardiogram QT prolongation is a well known risk factor for proarhythmic events, including sudden death. Lumefantrine is an aryl-amino alcohol antimalarial with some structural similarities to halofantrine. It is also, like halofantrine, lipophlic and hydrophobic, with very variable oral bioavailability leading to considerable inter-individual variability in plasma concentrations. However, unlike halofantrine, it proved to have no detectable cardiac effects over a wide range of plasma concentrations. In this study, there was no change in the electrocardiographic PR and QRS intervals after starting antimalarial treatment. Generally, small changes in QTc interval were noted, but they were similar to those reported in patients with malaria treated with other antimalarial drugs (and much less than those recorded after treatment with drugs known to prolong the QT interval), and they were unrelated to the plasma concentrations of lumefantrine. Several factors including age, heart rate, recovery from malaria, and, interestingly, study site (perhaps reflecting ethnic or nutritional differences between Karen and Thai subjects) were related to QT intervals, but drug levels were not. If lumefantrine had any significant effects on cardiac conduction or repolarization, then there should have been a relationship between concentration and effect, but none was found in this large and detailed study (Figure 1). Clear concentration-effect relationships are evident with halofantrine and quinidine, which have the greatest effects ventricular repolarization. Small but significant differences have been observed in the QT interval corrected by Bazett's formula between acute malaria and convalescence. \(^1\) Clear concentration-effect relationships are evident with halofantrine and quinidine, which have the greatest effects on cardiac conduction and repolarization. Small but significant differences have been observed in the QT interval corrected by Bazett's formula between acute malaria and convalescence. \(^1\) These are associated with a decrease in heart rate associated with defervescence. Dividing the QT interval by the square root of the R-R interval does not correct adequately for changes in heart rate since heart rate and QT/RR remain significantly correlated. \(^6\) Thus, the apparent malaria effect on ventricular repolarization may simply reflect heart rate changes. In any case, the effects are very small. In this study,
there was a small but statistically significant difference in QTc interval at the third day (after end of treatment), but this was similar for the 2 drugs, suggesting that it was related to recovery from malaria and not the antimalarial drugs themselves. Mefloquine has also been investigated in detail and is considered not to have clinically important effects on ventricular repolarization. Patients with pre-existing repolarization abnormalities may be more vulnerable to factors that prolong the QT interval. In this series, there was no relationship between baseline QTc interval and the fractional increase. Overall, these data provide strong evidence against a systematic effect of therapeutic doses of lumefantrine on cardiac conduction or repolarization.

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