COMPARISON OF THE CARDIAC EFFECTS OF THE ANTIMALARIALS CO-ARTEMETHER AND HALOFANTRINE IN HEALTHY PARTICIPANTS

MARGARETHA BINDSCHEDLER, GILBERT LEFÈVRE, PETER DEGEN, AND ANTOINE SIOUFI
Novartis Pharma Ltd., Research and Development Departments, Horsham, United Kingdom, Basel, Switzerland, and Rueil-Malmaison, France

Abstract. Co-artemether (Coartem®, Riamet®) is a tablet containing 20 mg artemether and 120 mg lumefantrine for treatment of falciparum malaria. Lumefantrine has some chemical similarities to halofantrine (Halfan®), an antimalarial known for QTc prolongation. Effects on the QTc interval of fed single oral doses of 500 mg halofantrine and 80/480 mg co-artemether were compared in 13 healthy males in a randomized double-blind crossover study. Electrocardiograms (ECGs) were recorded from 48 hours before dosing until 48 hours thereafter. The maximum QTc interval (QTc = QT/RR) was compared before and after treatment and between treatments, fitting a general linear model. Drug plasma concentrations were determined concomitantly. After halofantrine, all participants showed an increase in the QTc interval; the mean maximum increase was 28 ms. The length of the QTc interval was positively correlated to halofantrine exposure. The QTc interval remained unchanged after co-artemether. The difference between treatments was statistically significant. In conclusion, halofantrine caused a significant, exposure-dependent increase in the QTc interval. No such effect was seen with co-artemether.

Malaria is the cause of considerable morbidity and mortality in the developing world, and there is a clear need for new treatments, particularly as resistance to available drugs is increasing.1,2

Co-artemether (Coartem®, Riamet®), which was developed in China for the treatment of falciparum malaria, is an oral preparation containing 20 mg artemether and 120 mg lumefantrine (previously known as benflumetol) per tablet. Artemether, an artemisinin derivative, is characterized by a rapid onset of schizontocidal action resulting in fast relief from fever and fast parasite clearance. However, recrudescence is frequent when provided as a single agent, unless given for at least 5–7 days.3,4 By contrast, lumefantrine has a high cure rate when administered as a short treatment course of 2–3 days duration, but parasite and fever clearance is much slower than with artemether. Co-artemether combines the treatment advantages of both drugs, providing a short and simple antimalarial treatment likely to improve compliance. In areas of multidrug resistance and in nonimmune patients, the recommended dose regimen is 6 doses of 4 tablets each (80 mg artemether and 480 mg lumefantrine per dose) given over 60 hours. Otherwise, the recommended dose regimen is 4 doses of 4 tablets over 2 days.

Halofantrine (Halfan®, Riamet®) is one of the antimalarial compounds causing QTc prolongation at standard therapeutic doses (3 doses of 500 mg given at 6-hour intervals). Because lumefantrine has some chemical similarities to halofantrine, and QTc prolongation was reported after high-dose intramuscular treatment with artemether in animal experiments7 and in a clinical study in patients with severe malaria,9 a careful evaluation of co-artemether with regard to cardiac effects, particularly on the QTc interval, was warranted.

In the current study, the potential cardiac effects of co-artemether were evaluated and compared with those of halofantrine. Furthermore, the relationship between QTc interval and plasma drug concentration was explored for both compounds.

MATERIALS AND METHODS

Participants. Fourteen Caucasian healthy males (mean age = 33 years; age range = 24–49 years; mean weight = 79 kg; weight range = 69–90 kg; mean height = 181; height range = 174–189 cm) were recruited; at least 12 were required to complete both study periods. Individuals with cardiac disease or intolerance to the study drugs and those with relevant findings in physical examination, routine laboratory, or electrocardiogram (ECG), including a QTc interval > 440 ms, were not eligible for the study. The protocol was approved through an Ethics Committee at the University Hospital of Basel, Switzerland. All participants gave written informed consent.

On the basis of previous experience in malaria patients treated with co-artemether, 13 subjects who had completed the study were estimated to provide 80% power to detect a statistically significant difference in the QTc interval if the true underlying difference between treatments was 30 ms.

Study design and treatments. This was a single-center randomized double-blind, double-dummy, two-period crossover study comparing the cardiac effects of single oral doses of halofantrine and co-artemether in healthy males. Because of the long elimination half-life of several days for both lumefantrine9,10 and halofantrine,11,12 a 6-week washout period was required between treatments. No placebo control was included because a three-way crossover design was considered impracticable based on the long washout phase. Instead, repeated ECG recordings were performed under the same conditions and at the same time points as on treatment days in the 48 hours before each treatment.

Halofantrine (Halfan®, 250 mg tablets) and matching placebo were provided by Smith Kline Beecham, Germany. Co-artemether (Riamet®, tablets containing 20 mg artemether and 120 mg lumefantrine) and matching placebo were provided by Novartis Pharma AG, Switzerland. Co-artemether (or matching placebo) was administered at a single oral dose of 80/480 mg. Halofantrine (or matching placebo) was administered at a single oral dose of 500 mg. Treatments were given with 200 ml of water 15 ± 5 minutes after a standardized high-fat meal (composition: fat 354 kcal, proteins 112 kcal, carbohydrates 370 kcal) to increase absorption of both drugs.9,13 The aim was to achieve plasma concentrations similar to those observed in malaria patients after repeated dosing.

General study procedures. Participants were confined to the study site until completion of the 24-hour measurements...
after each treatment and had to return for further evaluations as indicated later. Blood was collected through a venous cannula (Venflon®) or by venipuncture. The participants had to abstain from strenuous physical activities and from alcohol from 72 hours before until 48 hours after each treatment. Caffeine-containing beverages were not allowed from 60 hours before treatment until 24 hours thereafter.

Pharmacodynamic (ECG) measurements. Twelve-lead ECGs were recorded after 10 minutes rest in the supine position immediately before treatment, hourly from 1–10 hours, and at 12, 15, 24, 34, and 48 hours after dosing. ECGs were also recorded under identical conditions and at the same time points in the 48 hours before each treatment. ECGs were recorded at a paper speed of 50 mm/sec followed by a tracing at 10 mm/sec for 30 sec for rhythm evaluation. ECGs were qualitatively assessed, and heart rate, PQ, QRS, and QTc interval (QTc = QT/√RR) were evaluated by a computer program (Hanover Hess). The investigator verified the computer evaluations while blinded, and intervals were remeasured manually in case of incorrect computer evaluation.

Pharmacokinetic measurements. Blood samples (5.5 ml each) for the determination of plasma concentrations of lumefantrine, artemether, its active metabolite dihydroartemisinin, and halofantrine were collected into lithium-heparinized tubes before treatment (0 hour) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 34, and 48 hours after dosing. The blood samples were immediately centrifuged at 2500 g during 5 minutes at room temperature. Plasma samples were snap-frozen on dry ice and stored at –70°C until analysis.

Artemether and dihydroartemisinin (DHA) plasma concentrations were analyzed by means of a reverse-phase high-performance liquid chromatography (HPLC) method using reductive electrochemical detection. The method was validated during the analyses using spiked plasma samples in the range 10–200 ng/ml. The recovery values (found vs. given concentrations) were in the range of 98–101% and the intra-assay coefficients of variation in the range of 6–7% for artemether. The corresponding values for DHA were 94–101% and 4–11%, respectively. The limit of quantitation was established at 10 ng/ml for both artemether and dihydroartemisinin.

Lumefantrine plasma concentrations were analyzed by means of an HPLC method with ultraviolet (UV) detection. The recovery values for the spiked plasma samples (range = 40–1,230 ng/mL) were in the range of 92–112% and coefficients of variation in the range of 10–25%. The limit of quantitation was established at 50 ng/ml.

Halofantrine plasma concentrations were analyzed by an HPLC method with UV detection. The recovery values for the spiked plasma samples (range 49–1,240 ng/ml) were in the range of 74–126% and coefficients of variation in the range of 9–22%. The limit of quantitation was established at 50 ng/ml.

Concentrations below limit of quantitation were taken as zero for pharmacokinetic calculations. The following model-independent parameters were determined from plasma concentration data: Cmax, highest observed plasma concentration; tmax, time to reach Cmax; AUC(0–48h), area under the plasma concentration-time curve over the time interval 0–48 hours, calculated by the trapezoidal method from 0 hour to the last time point with a concentration different from zero.

Statistical evaluations. In the primary analysis, the maximum QTc interval during the first 15 hours after each treat-

ment (QTcmax[0–15h]) was compared between co-artemether and halofantrine. In addition, the following secondary analyses were performed. The maximum QTc interval during 24–48 hours after each treatment (QTcmax[24–48h]) as well as the mean value calculated from QTcmax[0–15h] and the two neighboring measurements were compared between treatments. Furthermore, the maximum QTc interval observed during 48 hours before each treatment (QTcmax[48–60h]) was compared with the maximum QTc interval observed within 48 hours after each treatment (QTcmax[0–48h]).

Comparisons between treatments were carried out fitting a general linear model using the GLM procedure (SAS version 6.12). The models included sequence, subject within sequence, period, treatment effects, and the following two baseline values as covariate: QTc interval recorded immediately before treatment (time 0) and the pretreatment QTc value recorded at identical time as the analyzed posttreatment QTc value. For the comparison of the QTc interval before and after treatment, the model included subject, baseline (time 0), and the combined effects of period and treatment. Treatment difference was estimated using the ESTIMATE statement of the GLM procedure.

An exploratory pharmacokinetic-pharmacodynamic evaluation was performed for artemether, dihydroartemisinin, lumefantrine, and halofantrine by plotting the QTc interval against the respective plasma drug concentrations.

RESULTS

Study participants. Fourteen participants received at least one of the study treatments. One participant was withdrawn after the first treatment period (co-artemether treatment) as a result of an underlying medical condition unrelated to the study drug. Pharmacokinetic and safety data were evaluated for all participants. ECG data were analyzed for the 13 participants who completed both study periods.

Cardiac effects. Heart rates were comparable after treatment with halofantrine and co-artemether, and no clinically relevant study drug-related changes in heart rate were observed after either treatment. No clinically relevant effects on the PQ interval or QRS complex were seen after either treatment. The participant who was prematurely withdrawn from the study did not show any relevant change in QTc interval or any of the other ECG parameters.

QTc values before and after treatment with co-artemether or halofantrine for the 13 evaluable participants are displayed in Figure 1. Percentage changes of QTc from baseline (0h) for both co-artemether and halofantrine are displayed in Figure 2. Statistical results are summarized in Tables 1 and 2.

No clinically relevant changes in QTc interval were seen after administration of co-artemether. There was no marked difference in the mean QTc interval in the 48 hours before or after co-artemether treatment and no significant QTc prolongation was observed in any of the study subjects after treatment with co-artemether.

After treatment with halofantrine, the mean QTc interval increased by 28 ms (± 15.6 SD), reaching its maximum of 448 ms (± 19.9) 6 hours after dosing. The QTc-interval exceeded the upper normal range of 440 ms in all but one participant. In four, the QTc interval exceeded 460 ms. The maximum individual QTc prolongation was 495 ms. There was a statis-
tically significant increase in maximum QTc interval after halofantrine compared with pretreatment values. There was also a statistically significant difference of the maximum QTc intervals between treatment with co-artemether and halofantrine.

Nonspecific ST-T changes were observed in seven participants after treatment with halofantrine.

DISCUSSION

In this study, the cardiac effects of fed single oral doses of 80/480 mg co-artemether and 500 mg halofantrine, an anti-malarial known to prolong the QTc interval, were compared in healthy participants. Co-artemether had no effect on the QTc interval. In contrast, halofantrine caused a significant increase in the QTc interval, which is in line with data reported in the literature after standard treatment for falciparum malaria (i.e., three doses of halofantrine 8 mg/kg over 12 hours in children or 3 doses of 500 mg over 12 hours in adults). Matson and others observed a mean increase in the QTc interval of 40 ms in adult malaria patients receiving standard halofantrine treatment. Karbwang and others observed an increase in QTc interval in 27 of 29 adult malaria patients treated with halofantrine, with a greater than 25% increase in 8 patients. Sowunmi and others found a signifi-
cant increase in the QTc interval exceeding the upper normal range of 440 ms in 68% of 42 children treated with standard halofantrine. Ventricular arrhythmia and/or syncope in connection with QTc prolongation has been reported after standard21–24 and high-dose (3 doses of 24 mg/kg) halofantrine treatment.25 Such arrhythmia occurred mainly under conditions of preexisting QTc prolongation or in malaria patients pretreated with mefloquine.

QTc prolongation was previously observed in animals and in patients with severe malaria when artemether was administered at high intramuscular doses.7,8 However, well in line with the findings of the current study, to date no QTc prolongation has been reported after oral treatment with artemether despite its wide use.

Drug-induced QTc prolongation is usually concentration dependent. Halofantrine plasma concentrations in the current study were well in the range of, or in a few subjects even somewhat higher than, halofantrine plasma concentrations reported in malaria patients.11,12,19,25–27 As expected, the length of the QTc interval increased with increasing systemic exposure to halofantrine; however, even in those individuals with the lowest plasma concentrations (Cmax of approximately 1000 ng/ml), a clear increase in the QTc interval was seen. Likewise, increases in the QTc interval at halofantrine plasma concentrations of about 1,000 ng/ml or even lower can be found in the literature.19,25,27 Plasma concentrations of lumefantrine in the current study were comparable to those previously reported in Thai patients treated with four doses of co-artemether but generally lower than those observed in Chinese patients treated with four doses of co-artemether or patients treated with a six-dose regimen.9 Artemether concentrations were comparable to those found in clinical studies with co-artemether, whereas dihydroartemisinin concentrations were generally lower than in the clinical setting.9 Because the length of the QTc interval is related to the magnitude of drug exposure, QTc prolongation cannot definitely be ruled out for patients with higher exposure to lumefantrine or dihydroartemisinin than observed in the current study. However, in a drug interaction study, in which the effects on the QTc interval between a six-dose co-artemether regimen with or without mefloquine pretreatment were compared, no effects on the QTc interval were observed despite much higher exposure to co-artemether.10,28 In that study, artemether and dihydroartemisinin exposure was similar, and lumefantrine exposure in some participants was even higher than the exposure previously observed in malaria patients treated with four to six doses of co-artemether (Novartis Pharma Ltd., unpublished data).9,10,28,29

The ECG data reported for malaria patients treated with co-artemether are also highly reassuring. ECGs were recorded in more than 700 patients with falciparum malaria treated with co-artemether in comparative studies with various other antimalarials.30–32 The frequency of QTc prolongation observed after co-artemether was similar to or lower than

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**Table 3**

Pharmacokinetic parameters of artemether, dihydroartemisinin, lumefantrine, and halofantrine after single oral doses of co-artemether 80/480 mg or halofantrine 500 mg given after a high-fat meal

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cmax (ng/ml)</th>
<th>tmax (h)</th>
<th>AUC(0–48h) [ng/mlh]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether</td>
<td>59.8 (35.1)</td>
<td>2 (1–5)</td>
<td>174 (84.7)</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>49.4 (15.3)</td>
<td>2 (1–5)</td>
<td>160 (48.7)</td>
</tr>
<tr>
<td>Lumefantrine</td>
<td>4,456 (1,783)</td>
<td>6 (5–8)</td>
<td>69,879 (36,789)</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>2,154 (770)</td>
<td>5 (2–5)</td>
<td>17,483 (7,000)</td>
</tr>
</tbody>
</table>

Cmax and AUC are mean values ± SD; tmax is expressed as range.
that observed with chloroquine, mefloquine, or combined artesunate and mefloquine, antimalarials that themselves are not recognized to cause QTc prolongation.\textsuperscript{30–32} It is likely that the disease itself (e.g., by causing changes in heart rate and electrolyte disturbances) contributes to the cardiac effects observed in these patients. In contrast, treatment of falciparum malaria with the comparators quinine and halofantrine, both of which are known to prolong the QTc interval, produced clearly more frequent QTc prolongation than co-artemether.\textsuperscript{30} In the latter studies, quinine caused a QTc prolongation in 18.5% of the patients versus 3.5% under co-artemether, and halofantrine caused a QTc prolongation in 26% of the patients versus 8.3% under co-artemether.\textsuperscript{30} As in healthy subjects, in these malaria patients, the increase in the QTc interval was positively related to halofantrine plasma concentration (Novartis Pharma Ltd., unpublished data). On the other hand, no correlation was found between a wide range of lumefantrine plasma concentrations and the length of the QTc interval in the patients treated with co-artemether (Novartis Pharma Ltd., unpublished data),\textsuperscript{30} pointing also to the absence of a co-artemether-related QTc prolonging effect.

In conclusion, co-artemether at a fed single oral dose of 80/480 mg had no relevant cardiac effects in any participants in this study. In contrast, halofantrine at a fed single oral dose of 500 mg caused a significant increase in the QTc interval above the normal range in all but one participant and produced nonspecific ST-T changes in some. The length of the QTc interval was positively correlated to halofantrine plasma concentrations, and the maximum QTc prolongation was concurrent with the peak plasma concentration.

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Authors’ addresses: Margaretha Bindschedler, Novartis Horsham Research Center, Wimblehurst Road, Horsham, W-Sussex RH12 5AB, England; Gilbert Lefèvre and Peter Degen, Novartis Pharma AG, CH-4002 Basle, Switzerland; Antoine Sioufi, Novartis Pharma S.A., 2-4 rue Lionel Terray, F-92506 Rueil-Malmaison, France.
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