Am. J. Trop. Med. Hyg., 77(3), 2007, pp. 447–450

Short Report: Electrocardiographic Safety Evaluation of Dihydroartemisinin–Piperaquine in the Treatment of Uncomplicated falciparum Malaria

Oliver T. Mytton, Elizabeth A. Ashley, Leon Peto, Ric N. Price, Yar La, Rae Hae, Pratap Singhasivanon, Nicholas J. White, and François Nosten*

Shoklo Malaria Research Unit, Mae Sot, Thailand; Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Old Road, Headington, Oxford, United Kingdom; Menzies School of Health Research, Charles Darwin University, Darwin, Australia, Epicentre, Paris, France

Abstract. Dihydroartemisinin–piperaquine (DP) could become a leading fixed combination malaria treatment worldwide. Although there is accumulating evidence of efficacy and safety from clinical trials, data on cardiotoxicity are limited. In two randomized controlled trials in Thailand, 56 patients had ECGs performed before treatment, 4 hours after the first dose, and 4 hours after the last dose. The mean (95% CI) changes in QTc interval (Bazett's correction) were 2 (–6 to 9) ms and 14 (7 to 21) ms, respectively. These small changes on the third day of treatment are similar to those observed elsewhere in the convalescent phase following antimalarial treatment with drugs known to have no cardiac effects and are therefore likely to result from recovery from acute malaria and not the treatment given. At therapeutic doses, DP does not have clinically significant effects on the electrocardiogram.

INTRODUCTION

Dihydroartemisinin–piperaquine (DP) is a fixed combination antimalarial treatment developed in China. The excellent efficacy of this combination has been demonstrated in several large randomized controlled trials. DP has been very well tolerated.[1–4] Artemisinin derivatives are generally considered to be safe in terms of cardiotoxic potential, and although QTc prolongation (Bazett's correction) has been reported, particularly in toxicological evaluations in dogs with central nervous system abnormalities,[5,6] clinically significant changes have not been observed in the treatment of malaria.[7–9] Piperaquine is structurally similar to chloroquine, which has lethal cardiovascular toxicity in overdose and significant electrophysiological effects on the heart.[10] Cardiac electrophysiological studies show that chloroquine blocks the inward sodium current, I_{Na} (the class 1 effect), the L-type calcium current (I_{Ca}-L), and two potassium currents including the rapid delayed rectifier outward currents (I_{Kr}; the hERG channel) associated with QT prolongation. There are no corresponding electrophysiological data for piperaquine. In a study of 62 adults and children, in Cambodia, electrocardiographic (ECG) findings after DP treatment showed a significant lengthening of the mean QTc by 11 ms (95% CI 4–18).[11]

Various guidelines exist for the assessment of QT prolongation by noncardiovascular drugs. The U.S. Food and Drug Administration (FDA) sets a conservative threshold of concern for any drug that causes a mean increase in QTc of 5 ms and a high level of concern for an increase of 20 ms.[12] The European Society of Cardiology sets no absolute levels and, like the FDA, advocates other approaches to assessing the seriousness of QTc prolongation, such as categorizing the number of cases of QTc > 500 ms or absolute increases > 60 ms.[12,13]

Evaluation of QT interval changes is problematic in malaria because of systematic differences between the acute febrile admission before antimalarial drugs are given and early convalescence, when the peak antimalarial drug concentrations occur and the repeat ECG measurements are made.[14] At presentation, patients are usually anxious, fasting, and febrile with increased autonomic tone, and a raised heart rate. This contrasts with the relaxed, fed, supine afebrile state 3 days later, when most antimalarial treatments finish and antimalarial drug concentrations are at their highest. It has been argued that this systematic reduction in sympathetic activity with recovery leads to a consistent increase in the QT interval, which has been mistakenly ascribed to antimalarial drug effects.[14] Studies over a short period of time or in healthy volunteers are preferable. Although Bazett's formula ($QTc = QT/RR^{0.5}$) is most commonly used to rate-correct the QT interval, it is inaccurate at high and low heart rates.[10,12,15] Fridericia's cube-root correction ($QTc = QT/RR^{0.3}$) is often preferred.[12] In the Karen population, we found the optimal rate correction was $QTc = QT/RR^{0.4}$ (Karen formula).[10]

This study was part of two randomized trials of DP in the treatment of uncomplicated malaria on the northwestern border of Thailand during 2002 and 2003, which have been reported elsewhere.[3,4] Ethical approval for both studies was obtained from the Faculty of Tropical Medicine, Mahidol University, Bangkok, and the Oxford Tropical Research Ethics Committee. Patients were Karen or Burmese adults and children with symptomatic slide-proven uncomplicated falciparum malaria. They were given one of two dosing regimes of DP (Artekin, Holleykin Pharmaceutical Co. Ltd, Guangzhou, China), total dose 7 mg/kg body weight of dihydroartemisinin and 55 mg/kg piperaquine, split into four doses at 0 hours, 8 hours, 24 hours, and 48 hours or into three doses at 0, 24, and

TABLE 1

Correlation between RR interval and QTc interval for the different methods of QT interval correction

	Bazett's		Karen		Fridericia's	
Time of ECG	Pearson correlation coefficient	*P* value	Pearson correlation coefficient	*P* value	Pearson correlation coefficient	*P* value
0 hours	–0.347	0.009	–0.097	0.467	0.095	0.484
4 hours	–0.340	0.010	0.068	0.621	–0.111	0.414
52 hours	–0.050	0.716	0.228	0.091	0.397	0.002

Each method involves QT correction for heart rate by dividing the QT interval by a power of the RR interval; for Bazett's, this is 0.5; for the Karen it is 0.4; and for Fridericia's, it is 0.33.

* Address correspondence to François Nosten, Shoklo Malaria Research Unit, 68/30 Ban Toong Road, P.O. Box 46, Mae Sot, 63110, Tak, Thailand. E-mail: smru@tropmedres.ac

TABLE 2
Number of readings with QTc increases at 4 hours and 52 hours, using the three different methods of QT interval correction

QTC prolongation from baseline (ms)*	Bazett's		Karen		Fridericia's	
	4 hours	52 hours	4 hours	52 hours	4 hours	52 hours
< 30	49 (87.5)	42 (75.0)	50 (89.2)	34 (60.7)	49 (87.5)	28 (50.0)
30–60	5 (8.9)	11 (19.6)	5 (8.9)	16 (28.6)	6 (10.7)	20 (35.7)
> 60	2 (3.6)	3 (5.4)	1 (1.8)	6 (10.7)	1 (1.8)	8 (14.3)

Percentages shown in parentheses. Bazett's, Karen, and Fridericia's are different forms of QT correction for heart rate, calculated by dividing the QT interval by a power of RR interval; for Bazett's, this is 0.5; for the Karen it is 0.4; and for Fridericia's, it is 0.33.
* Cutoffs used are taken from FDA guidelines.

48 hours. ECG monitoring was possible at only one site. All patients randomized to receive DP had a standard 12-lead ECG recorded (Autocardiner FCP-2155; Fukuda Denshi Co., Ltd., Tokyo, Japan), tracing at 25 mm/s paper speed, at baseline (0 hours). Repeat ECGs were recorded at 4 hours and 52 hours (4 hours after the first and last doses of DP). The QT and RR intervals were read manually in lead II, taking the mean of at least three readings, following FDA guidelines.[12] A second reader independently read all ECGs with a prolonged QTc, all ECGs with a QTc prolongation > 50 ms, and an additional set of ECGs chosen at random, such that a total of 20% of ECGs were checked. A third reader adjudicated on any disagreement between the first two readers.

The QT interval was corrected for heart rate using Bazett's formula, Fridericia's formula, and the Karen formula. The JTc interval was calculated: (QT interval – QRS interval)/$RR^{0.4}$, to separate effects on depolarization from prolongation in repolarization. Paired *t*-tests were used to compare the mean PR, QRS, JTc, and QTc intervals between 0 and 4 hours and between 0 and 52 hours. The 95% CI for the changes in QTc were derived from the standard error of the difference of the two means. The Pearson correlation coefficient was used to test for an association between the RR interval and QTc, for each method of rate correction, to determine the correction least dependent on heart rate. Using this method, the proportions of ECGs with a prolonged QTc interval (QTc > 450 ms), with an increase > 60 ms, or with an increase > 25% are presented.[12]

Data are presented on 56 patients (44 males and 12 females) with a median age (range) of 18 (6–60) years. One patient was excluded because the QT intervals could not be interpreted due to a poor trace. The median (range) heart rate at baseline was 95.5 (67–134) bpm, compared with 86 (60–120) bpm, 4 hours after the first dose ($P < 0.001$), and 69.5 (42–104) bpm, 52 hours after the first dose ($P < 0.001$). There was slight prolongation of the mean (SD) PR interval from 132 (14) ms at the baseline to 135 (15) ms ($P = 0.040$) at 4 hours, and 141 (16) ms ($P < 0.001$) at 52 hours. There was no PR prolongation > 200 ms. The mean (SD) QRS interval was unchanged, measuring 83 (12) ms at 4 hours ($P = 0.226$) and 83 (12) ms at 52 hours ($P = 0.281$), compared with 82 (11) ms at baseline.

The best correction for the QTc was the Karen formula, which resulted in the weakest correlation between the RR interval and the QTc (Table 1). There was no significant change in the mean QTc at 4 hours (Bazett's QTc [95% CI] = +2 [–6 to 9] ms, $P = 0.663$; Karen formula QTc = +1 [–5 to 9] ms, $P = 0.622$; Fridericia's QTc = +1 [–5 to 9] ms, $P = 0.629$) and a small increase at 52 hours (Bazett's QTc [95% CI] = +14 [7–14] ms, $P < 0.001$; Karen formula QTc = +24 [16–31] ms, $P < 0.001$; Fridericia's QTc = +29 [22–38] ms, $P < 0.001$), from baseline (mean QTc Bazett's = 407 ms; Karen formula = 390 ms; Fridericia's = 380 ms). There were similar changes observed in the mean JTc [95% CI], at 4 hours (0 [–8 to 8] ms, $P = 0.939$) and at 52 hours (30 [22–39] ms, $P < 0.001$) from baseline (294 ms).

The numbers of patients with QTc lengthening (defined as > 30 ms and > 60 ms, as specified by the FDA) are shown in Table 2. Table 3 shows the number of prolonged QTc readings at baseline, 4 hours, and 52 hours. The longest QTc observed was 520 ms at baseline, but this did not increase, measuring 520 ms at 4 hours and 481 ms at 52 hours. The greatest increase was 107 ms from 387 ms at baseline to 383 ms at 4 hours and 494 ms at 52 hours, in a 19-year-old male, the only patient to have a QTc prolongation > 25%. No patient, with a normal baseline QTc, had abnormal readings at both 4 and 52 hours. A total of 684 patients were treated with DP and followed. Within this group there was one sudden death within 24 hours of starting treatment; however, this was ascribed to severe malaria. No arrhythmias or abnormal ECG findings were documented in this group.

The electrophysiology findings presented here suggest that DP does not cause clinically relevant cardiotoxicity. Although the mean prolongation in the QTc of 14 ms (Bazett's) ob-

TABLE 3
Proportion of prolonged QTc readings at baseline, 4 hours, and 52 hours, using the three different methods of QT interval correction

QTc*	Bazett's (*n*)			Karen (*n*)			Fridericia's (*n*)		
	Baseline	4 hours	52 hours	Baseline	4 hours	52 hours	0 hours	4 hours	52 hours
< 450	54 (96.4)	51 (91.1)	50 (89.3)	55 (98.2)	54 (96.4)	53 (94.6)	55 (98.2)	55 (98.2)	53 (94.6)
450–479	1 (1.8)	3 (5.4)	4 (7.1)	0 (0)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	2 (3.6)
480–500	0 (0)	1 (1.8)	2 (3.6)	0 (0)	0 (0)	2 (3.6)	1 (1.8)	1 (1.8)	1 (1.8)
> 500	1 (1.8)	1 (1.8)	0 (0)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)

Percentages shown in parentheses. Bazett's, Karen, and Fridericia's are different forms of QT correction for heart rate, calculated by dividing the QT interval by a power of the RR interval; for Bazett's, this is 0.5; for the Karen it is 0.4; and for Fridericia's, it is 0.33.
* Cutoffs used are taken from FDA guidelines.

TABLE 4
Maximum observed mean QTc prolongation relative to baseline associated with different antimalarial drugs

Drug (no. of subjects)	Mean change in QTc (Bazett's) ms (95% CI)	Author (year)	Treated for malaria
Atovaquone–proguanil* (n = 20)	–6 (–30 to 8)	Gupta and others (2005)[18]	Yes
Artemether–mefloquine (n = 49)	8	van Vugt and others (1999)[7]	Yes
Artemether–lumefantrine (n = 150)	7	van Vugt and others (1999)[7]	Yes
Artemether–lumefantrine* (n = 60)	11 (–1 to 23)	von Seidlein and others (1997)[8]	Yes
Atovaquone–proguanil–artesunate* (n = 22)	11 (–4 to 25)	Gupta and others (2005)[18]	Yes
Sulfadoxine–pyrimethamine* (n = 37)	12 (0 to 24)	von Seidlein and others (1997)[8]	Yes
Dihydroartemisinin–piperaquine (n = 62)	11 (4 to 18)	Karunajeewa and others (2003)[11]	Yes
Dihydroartemisinin–piperaquine (n = 52)	15 (5 to 25)	Mytton and others (2007)	Yes
Chloroquine* (n = 42)	20 (8 to 32)	von Seidlein and others (1997)[8]	Yes
Halofantrine* (n = 42)	41 (36 to 46)	Sowunmi and others (1998)[21]	Yes
Halofantrine* (n = 24)	45 (33 to 57)	Touze and others (1996)[22]	Yes
Halofantrine† (n = 60)	63 (54 to 72)	Nosten and others (1993)[16]	Yes
Quinine* (n = 15)	41 (28 to 54)	White and others (1983)[20]	Yes
Quinine‡ (n = 15)	22 (7 to 37)	Sheldon and others (1995)[23]	No
Quinine (n = 8)	60	Karbwang and others (1993)[19]	No

* Values are calculated based on the published maximum mean QTc and standard deviation observed during treatment in comparison with baseline.
† Unpublished data (Nosten, personal communication, 2007).
‡ Values are from adult patients with ≥ 30 premature ventricular complexes or a history of sustained monomorphic VT.

served on the third day of illness is greater than the FDA's conservative threshold of concern for cardiotoxicity, it did not breach the level for high concern. Importantly, the QTc prolongation observed is comparable with that observed at this time with other antimalarials, shown in Table 4, using the same correction (Bazett's). This includes drugs with no known cardiac effects, which suggests that QT prolongation may have resulted from recovery from malaria and be unrelated to drug treatment. The value is less than the prolongation reported with chloroquine, the most widely used antimalarial, and substantially less than that associated with halofantrine, which is associated with sudden death.[16] QTc prolongations > 60 ms were within the bounds of normal daily variation in the QTc (up to 75–100 ms).[10] The observed increases in the QTc intervals were due to JT prolongation (i.e., repolarization) rather than QRS prolongation (depolarization) in contrast to chloroquine, which produces predominantly QRS prolongation.[17] Quinidine and halofantrine, which are associated with a significant risk of arrhythmia, cause significant JTc prolongation of much greater magnitude than observed with DP treatment but little QRS prolongation.[16,19,20]

Whether the observed QTc/JTc prolongation is a drug effect, an effect of malaria, or a response in recovery from a febrile illness remains uncertain.[7,11,14,15] The relatively homogenous changes in the QTc for a range of structurally unrelated antimalarials suggest the latter. The PR interval was significantly prolonged at 52 hours, this would be expected with a fall in the heart rate and the magnitude of change is not clinically meaningful

In a population PK evaluation of piperaquine, from the same study, it was estimated that peak concentrations of piperaquine occurred 8 hours after dosing (K. Stepniewska, unpublished data). It is possible that more profound changes in QTc may have been missed, although our estimate of QTc prolongation is similar to 11 ms observed for DP by others.[11] Larger studies in patients of all ages, including healthy volunteers, with concomitant piperaquine drug assay would strengthen the safety data.

Although some QT prolongation has been observed, the risk appears to be similar to other antimalarials and considerably less than that observed with drugs with clinically relevant cardiotoxicity. The absence of adverse cardiac events or significant ECG abnormalities in this series of 56 patients or the Cambodian series is reassuring. DP is one of the leading antimalarial candidates available and is likely to be deployed on a large scale once it has been registered internationally. The accumulating evidence of high efficacy and safety of this drug suggests that this process should be expedited.

Received December 9, 2006. Accepted for publication May 6, 2007.

Acknowledgments: We thank all the patients and staff of the Shoklo Malaria Research Unit who participated in these studies.

Financial support: The studies were partially supported by the Medicines for Malaria Venture (MMV). The Shoklo Malaria Research Unit is part of the Mahidol–Oxford Tropical Medicine Research Unit funded by the Wellcome Trust of Great Britain.

Authors' addresses: Oliver T. Mytton, Elizabeth A. Ashley, Leon Peto, Yar La, Rae Hae, and François Nosten, Shoklo Malaria Research Unit, P.O. Box 46 Mae Sot, Thailand; Telephone: +66 55 545 021, E-mail: SMRU@tropmedres.ac. Elizabeth A. Ashley, Nicholas J. White, Pratap Singhasivanon, and François Nosten, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. Nicholas J. White, Elizabeth A. Ashley, and François Nosten, Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Old Road, Headington, Oxford, United Kingdom. Ric N. Price, Menzies School of Health Research, Charles Darwin University, Darwin, Australia. Elizabeth A. Ashley, Epicentre, Paris, France.

Reprint requests: François Nosten, Shoklo Malaria Research Unit, 68/30 Ban Toong Road, P.O. Box 46, Mae Sot, 63110, Tak, Thailand, Telephone: +66 55 545021, Fax: +66 55 545020. E-mail: smru@tropmedres.ac.

REFERENCES

1. Denis MB, Davis TM, Hewitt S, Incardona S, Nimol K, Fandour T, Poravuth Y, Lim C, Socheat D, 2002. Efficacy and safety of dihydroartemisinin–piperaquine (Artekin) in Cambodian children and adults with uncomplicated falciparum malaria. *Clin Infect Dis 35:* 1467–1476.
2. Tran TH, Dolecek C, Pham PM, Nguyen TD, Nguyen TT, Le HT, Dong TH, Tran TT, Stepniewska K, White NJ, Farrar J, 2004. Dihydroartemisinin–piperaquine against multidrug-resistant *Plasmodium falciparum* malaria in Vietnam: randomised clinical trial. *Lancet 363:* 18–22.

3. Ashley EA, Krudsood S, Phaiphun L, Srivilairit S, McGready R, Leowattana W, Hutagalung R, Wilairatana P, Brockman A, Looareesuwan S, Nosten F, White NJ, 2004. Randomized, controlled dose-optimization studies of dihydroartemisinin–piperaquine for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *J Infect Dis 190:* 1773–1782.
4. Ashley EA, McGready R, Hutagalung R, Phaiphun L, Slight T, Proux S, Thwai KL, Barends M, Looareesuwan S, White NJ, Nosten F, 2005. A randomised controlled study of a simple once daily regimen of dihydroartemisinin–piperaquine for the treatment of uncomplicated multi-drug resistant falciparum malaria. *Clin Infect Dis 41:* 425–432.
5. Classen W, Altmann B, Gretener P, Souppart C, Skelton-Stroud P, Krinke G, 1999. Differential effects of orally versus parenterally administered qinghaosu derivative artemether in dogs. *Exp Toxicol Pathol 51:* 507–516.
6. Brewer TG, Grate SJ, Peggins JO, Weina PJ, Petras JM, Levine BS, Heiffer MH, Schuster BG, 1994. Fatal neurotoxicity of arteether and artemether. *Am J Trop Med Hyg 51:* 251–259.
7. Van Vugt M, Ezzet E, Nosten F, Gathmann I, Wilairatana P, Looareesuwan S, White NJ, 1999. No evidence of cardiotoxicity during antimalarial treatment with artemether–lumefantrine. *Am J Trop Med Hyg 61:* 964–967.
8. Von Seidlen L, Jaffar S, Greenwood BM, 1997. Prolongation of the QTc in African children treated for falciparum malaria. *Am J Trop Med Hyg 56:* 494–497.
9. Hien TT, Day NPJ, Phu NH, Mai NT, Chau TT, Loc PP, Sinh DX, Choung LV, Vinh H, Waller D, Peto TEA, White NJ, 1996. Controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria treated with artemsinin derivatives. *Am J Trop Med Hyg 60:* 936–942.
10. Yap YG, Camm AJ, 2003. Drug induced QT prolongation and torsade de pointes. *Heart 89:* 1363–1372.
11. Karunajeewa H, Lim C, Hung T-Y, Ilett KF, Denis MB, Socheat D, Davis TME, 2003. Safety evaluation of fixed combination piperaquine plus dihydroartemisinin (Artekin) in Cambodian children and adults with malaria. *Br J Clin Pharmacol 57:* 93–99.
12. Food and Drug Administration, 2005. *Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs.* Rockville, MD: FDA.
13. Haverkamp W, Breithard G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R, and other speakers in the sessions and chairs of the workshops, 2000. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. *Eur Heart J 21:* 1216–1231.
14. White NJ, 2007. The cardiotoxicity of the antimalarial drugs. *Lancet Infect Dis 7:* 549–558.
15. Price RN, Nosten F, White NJ, 1998. Prolongation of the QTc interval in African children treated for falciparum malaria (letter; comment). *Am J Trop Med Hyg 59:* 503.
16. Nosten F, ter Kuile F, Luxemburger C, Woodrow C, Kyle D, Chongsuphajaisiddhi T, White NJ, 1993. Cardiac effects of antimalarial treatment with halofantrine. *Lancet 341:* 1054–1056.
17. Looareesuwan S, White NJ, Chanthavanich P, Edwards G, Nicholl DD, Bunch C, Warrell DA, 1986. Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol 22:* 31–36.
18. Gupta RK, Van Vugt M, Paiphun L, Slight T, Looareesuwan S, White NJ, Nosten F, 2005. Short report: no evidence of cardiotoxicity of atovaquone–proguanil alone or in combination with artesunate. *Am J Trop Med Hyg 73:* 267–278.
19. Karbwang J, Davis TM, Looareesuwan S, Molunto P, Bunnag D, White NJ, 1993. A comparison of the pharmacokinetic and pharmacodynamic properties of quinine and quinidine in healthy Thai males. *Br J Clin Pharmacol 35:* 265–271.
20. White NJ, Looareesuwan S, Warrell DA, 1983. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. *J Cardiovasc Pharmacol 5:* 173–175.
21. Sowunmi A, Falade CO, Oduola AMJ, Ogundahunsi OAT, Fehintola FA, Gbotosho GO, Larcier P, Salako S, 1998. Cardiac effects of halofantrine in children suffering from acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg 92:* 446–448.
22. Touze JE, Bernard J, Keundjian A, Imbert P, Vigeur A, Chaudet A, Doury JC, 1996. Electrocardiographic changes and halofantrine plasma level during acute falciparum malaria. *Am J Trop Med Hyg 54:* 225–228.
23. Sheldon R, Duff H, Koshman ML, 1995. Antiarrhythmic activity of quinine in humans. *Circulation 92:* 2944–2950.