Cardiotoxicity of antimalarial drugs

Nicholas J White

There are consistent differences in cardiovascular state between acute illness in malaria and recovery that prolong the electrocardiographic QT interval and have been misinterpreted as resulting from antimalarial cardiotoxicity. Of the different classes of antimalarial drugs, only the quinolines, and structurally related antimalarial drugs, have clinically significant cardiovascular effects. Drugs in this class can exacerbate malaria-associated orthostatic hypotension and several have been shown to delay ventricular depolarisation slightly (class 1c effect), resulting in widening of the QRS complex, but only quinidine and halofantrine have clinically significant effects on ventricular repolarisation (class 3 effect). Both drugs cause potentially dangerous QT prolongation, and halofantrine has been associated with sudden death. The parenteral quinoline formulations (chloroquine, quinine, and quinidine) are predictably hypotensive when injected rapidly, and cardiovascular collapse can occur with self-poisoning. Transiently hypotensive plasma concentrations of chloroquine can occur when doses of 5 mg base/kg or more are given by intramuscular or subcutaneous injection. At currently recommended doses, other antimalarial drugs do not have clinically significant cardiac effects. More information on amodiaquine, primaquine, and the newer structurally related compounds is needed.

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Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand and Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, UK (Prof N J White FRS)

Correspondence to:
Prof Nicholas J White,
Faculty of Tropical Medicine,
Mahidol University,
420/6 Rajvithi Road,
Bangkok 10400, Thailand.
Tel +66 2 354 9172;
fax +66 2 354 9169;
nickw@tropmedres.ac

Introduction

Antimalarial drugs are prescribed and self-medicated on a vast scale in the tropical areas of the world. In terms of human exposure, the 4-aminoquinoline chloroquine has been arguably the most widely used drug ever because of its long terminal elimination half-life (1–2 months). The first antimalarial drugs to be introduced into western medicine were the cinchona alkaloids, originally as bark or bark extracts containing a mixture of several different compounds. One of these alkaloids was quinidine—the prototype for agents causing prolongation of the electrocardiographic QT interval (often called the "quinidine effect", and the hallmark of class 3 antiarrhythmic drugs)[1] (figure 1). Quinidine was used mainly as an anti-arrhythmic (for the maintenance of sinus rhythm in patients prone to atrial flutter or fibrillation, and for the prevention of ventricular tachycardias), and not as an antimalarial drug throughout most of the 20th century. It was also well known on occasions to cause tachyarrhythmias (quinidine syncope) and has recently been replaced by less toxic alternatives.

From the 1920s onwards the quinoline structure was modified sequentially as a succession of synthetic antimalarial drugs were produced. The most important of these were pamaquine (1926), mepacrine (1932), chloroquine (1934), amodiaquine (1951), primaquine (1952), mefloquine (1963), halofantrine (1966), and in the past 30 years piperaquine, lumefantrine, and pyronaridine. All of these drugs interfere with the intraparasitic detoxification of haem, although there are important differences in the antiparasitic activities of the various drugs. The lethality of chloroquine in overdose, the quinidine effect,[2] and the belated discovery that halofantrine causes marked QT prolongation[3] and sudden death, well after its registration by several regulatory authorities, have focused attention on the potential cardiotoxicity of the antimalarial drugs. Regulatory authorities and drug developers have become particularly concerned about QT prolongation.[4–7] Several of the quinoline drugs and other compounds related to chloroquine, quinidine, and halofantrine are potentially hypotensive, and have small electrocardiographic effects, but have not been associated with significant cardiotoxicity in clinical practice. One should emphasise that their safety in patients with pre-existing cardiovascular disease, receiving other cardioactive drugs, has not been established because nearly all patients with malaria are young with otherwise normal hearts. Such patients in endemic areas form the bulk of the evidence base for antimalarial safety. This Review concentrates on acute cardiotoxicity in the context of malaria treatment and summarises current clinical and laboratory information.

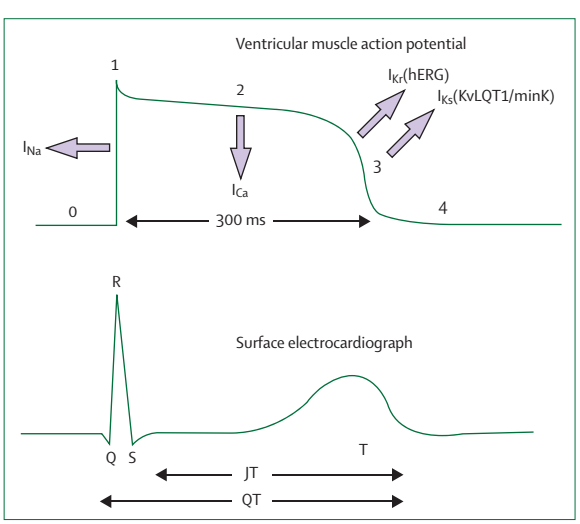

***Figure 1*: The individual ventricular cardiac myocyte action potential with corresponding ion currents, and its surface representation in the electrocardiograph**

I_{Kr}=rapid component of the delayed rectifier. I_{Ks}=slow component of the delayed rectifier. hERG=human ether-a-go-go-related gene. At rest the cardiac myocyte has a negative membrane potential. Stimulation results in opening of voltage-gated ion channels and an influx of cations (upper panel). First sodium (phase 1; I_{Na}) then calcium (phase 2; I_{Ca}) enter the cell causing depolarisation. In phase 3 there is a net outward movement of potassium ions (rectifying current) via I_{Kr} and I_{Ks} restoring the membrane potential. These changes are reflected in the surface electrocardiogram (lower panel).

The QT interval

Prolongation of the electrocardiograph QT interval reflects prolongation of ventricular repolarisation and thus the effective refractory period. Many factors affect the duration of ventricular repolarisation. The QT interval varies from beat to beat, in daytime compared with night time, and from day to day. It is affected by age, sex, autonomic tone, myocardial ischaemia, electrolyte concentrations, and importantly by several different classes of drugs. This pharmacological property is used to prevent ventricular arrhythmias, but it could also cause them. Heterogeneous prolongation of ventricular repolarisation predisposes to intraventricular circuits of depolarisation that manifest as potentially lethal polymorphic malignant ventricular tachyarrhythmias (torsades de pointes; TdP). Repolarisation of cardiac ventricular myocytes is mainly caused by outward currents of potassium ions (figure 1). One of the most important outward currents is the delayed rectifier current of potassium ions, I_K, which has rapidly and slowly activating components (I_{Kr} and I_{Ks}, respectively).[8] Activation of I_{Kr} leads to initiation of repolarisation of the cardiac action potential. The human ether-a-go-go-related gene (hERG) on chromosome 7 q35-36 encodes the pore-forming subunits of the hERG channel, which carries the rapidly activating delayed rectifier current of potassium ions through I_{Kr} (figure 1).[9,10] Impaired I_{Kr} function leads to intracellular accumulation of potassium ions and consequent delay in ventricular repolarisation (reflected electrocardiographically as prolongation of the QT interval).

Mutation of the hERG gene is a common cause of the inherited long QT syndrome, a disorder of cardiac repolarisation that predisposes affected individuals to TdP and sudden death. hERG has been identified as the target for drugs (eg, quinidine and other class 3 antiarrhythmics, phenothiazines, tricyclic antidepressants, some antihistamines, some antiemetics, macrolides, ketolides, fluoroquinolones, azole antifungals, pentamidine, etc) that prolong the QT interval and can cause TdP.[7–10] In general, drugs bind and then inhibit the channel only when the voltage-gated channels are open. Several unrelated drug classes are associated with QT prolongation and, especially in individuals with a hereditary long QT interval, can cause ventricular tachycardia, particularly TdP, and sudden death. Although many drugs predispose to TdP, in documented cases usually more than one predisposing factor is present—eg, electrolyte abnormalities (hypokalaemia, hypomagnesaemia), myocardial ischaemia, female sex, and inherited long QT syndrome, or there is a drug interaction (either a metabolic interaction or a second drug also causing QT prolongation).

Malaria

In assessing iatrogenic effects of antimalarial drugs on the heart, one must also consider the underlying disease effects. Orthostatic hypotension is common in febrile illnesses such as malaria, and can be exacerbated by quinoline antimalarials.[11,12] Autonomic postural responses are blunted.[12] There are consistent differences in sympathetic tone when comparing the patient's acute admission to hospital with malaria, associated with arousal, stress, discomfort, anxiety, and usually fasting, and the recovery phase when the patient is relaxed, comfortable, supine in bed, and has often resumed eating.[13] Stress, anxiety, discomfort, and the consequent increased sympathetic tone increases heart rate, and accelerates conduction and repolarisation,[14–17] reflected electrocardiographically as QT shortening. The potentially arrhythmogenic asynchrony of ventricular repolarisation is also increased, reflected electrocardiographically as QT dispersion,[18] although the relation between dispersion and arrhythmogenic potential is weak.[19] Thus, as the patient recovers from malaria, there will be a consistent reduction in heart rate and lengthening of the QT interval as a result of decreased autonomic (mainly sympathetic) tone which is independent of antimalarial treatment. Yet this effect has often been attributed to the direct cardiac effects of the antimalarial drugs.

Malaria is an acute illness associated with non-specific fever, sinus tachycardia, and a reduced systemic vascular resistance, largely attributable to release of pro-inflammatory cytokines. Severe falciparum malaria has a unique pathology characterised by widespread sequestration of erythrocytes containing mature malaria parasites and consequent microvascular obstruction. Although *Plasmodium falciparum* sequesters in the myocardial microvasculature, significant myocardial dysfunction or arrhythmias are very unusual in severe malaria.[20] Fever increases the heart rate; for each 1ºC increase in core temperature heart rate increases by 8·5 bpm. With successful treatment the pulse rate declines as the symptoms and other signs resolve. Heart rates can be relatively slow immediately after defervescence in supine patients. Small changes in electrocardiographic intervals have been noted when patients have received antimalarial treatments (eg, sulfadoxine-pyrimethamine) which are very unlikely to affect the heart.[21,22] Indeed, nearly all studies of antimalarial drugs report some prolongation of the QT interval in the days after the start of treatment. This observation suggests that malaria (or more precisely the difference between acute illness and recovery) can have small but significant differential effects on myocardial electrophysiology.

Another problem that pervades the published work has been the systematic error introduced with rate corrections, such as Bazett's correction for the QT interval. This particular adjustment does not correct adequately, tending to overestimate the QT interval at rapid heart rates and to underestimate the QT interval at low heart rates. Prolongation of the QT interval reflects either widening of the QRS (depolarisation) or prolongation of the JT (repolarisation) interval, or both (figure 1). Prolongation of the JT interval is associated with an increased risk of lethal ventricular tachycardia.[6] The QT interval shortens as

heart rate increases, so for comparisons (particularly of antimalarial drugs in malaria), rate effects are a consistent confounder. Ideally, drug effects should be compared at the same heart rate, which means studying volunteers, but studies in volunteers would not detect any drug–disease interaction.

There is still uncertainty as to the best approach to rate correction. Bazett's correction is the most widely used correction. This divides the QT interval by the square root of the RR interval (QTc=QT/(RR)$^{0.5}$. This calculation leaves a residual positive correlation between heart rate and the corrected interval (QTc).[23–27] As a result, changes in heart rate are associated with changes in the QTc interval, which will usually differ between admission and subsequent days. Better correction is obtained with Fridericia's correction (QT/RR$^{0.33}$), Hodges correction (QT+1·75[heart rate–60]), or the Framingham correction (QT+0·154[1–RR]); none of these is entirely satisfactory. Corrections in children and adolescents differ from those in adults.[28] In the only study of malaria where rate correction has been studied specifically, a slightly different correction—QT/(RR)$^{0.4}$—was found to provide the least dependence of QT interval on heart rate.[22,29] As mentioned, changes in posture, level of arousal, level of autonomic activation, autonomic function, time of day, and fever itself all have independent effects on the QT interval, apart from effects on rate,[13–18] which also result in systematic changes as the patient recovers (table 1). The QT interval even increases after meals.[30] Thus, to investigate antimalarial drug effects on the QT interval, studies over a short time interval (<12 h) in malaria, or studies in healthy volunteers, are preferable to comparisons of intervals over days as the patient recovers from illness. Ideally, blood or plasma concentrations of the antimalarial drug (both parent and any active metabolites) should be measured in all studied individuals (and obviously other drugs such as macrolide, ketolide, or quinolone antibiotics[7,31] or antiemetics that affect myocardial depolarisation or repolarisation must be avoided). Failure to show any relation between drug levels (parent drug and active metabolites) and any putative cardiovascular effects in an adequately powered study is strong evidence against significant toxicity within the normal therapeutic range. Although dysrhythmias are very rare in malaria, one should note that some ion channel abnormalities (so-called channelopathies) might only become evident during fever,[32] and stress and increased sympathetic tone are also arrhythmogenic.

There are also methodological concerns in many studies; manual reading of electrocardiographic intervals at a paper speed of 25 mm/s is associated with substantial measurement errors. In addition to the paper speed, the leads chosen and the technique (especially for the definition of the end of the T wave) also affect the result. Automated methods have become more popular in recent years, but variance, especially for QT measurement, may be greater with these.[33] Finally, there is a tendency, particularly in regulatory studies, to record serial electrocardiographs and report the greatest deviation (eg, the greatest prolongation of QT interval found among several recordings) from the baseline value.[34] Such reporting creates a random sampling error in that the more samples that are taken, the greater the maximum value is likely to be, on top of the systematic errors in comparing acute with convalescent values. The more the imprecision of the measurement, the greater will be the deviation.

	Effect on ECG QTc interval
Reduced anxiety and stress	Prolongation
Supine	Prolongation
Eating	Post-prandial prolongation
Defervescence	Prolongation
Bazett's correction	Shortens at low heart rates
Multiple comparisons: choosing the longest convalescent value	Prolongation

ECG=electrocardiogram.

Table 1: **Factors independent of antimalarial cardiac action that affect the QT interval during the recovery phase from malaria, when compared with acute admission**

Quinine and quinidine

Quinine is the laevorotatory diastereomer of quinidine, but differs from it in many pharmacological respects. In terms of free drug concentration, quinine is about three to four times less active as an antimalarial drug.[35] Both drugs have alpha-blocking activity that can cause hypotension. This effect has been particularly studied for quinidine, which blocks the α_1ARs receptor subtype.[36,37] Lethal hypotension resulting from both vasodilatation and negative inotropism can follow rapid intravenous injection. The hypotensive potential of the cinchona alkaloids following intravenous injection was recognised when this method of administration was introduced over 100 years ago. Until the 1940s, parenteral quinine was given by intravenous or intramuscular injection. Transiently high plasma concentrations during the distribution phase caused hypotension. The slow intravenous infusion method, introduced by Strahan[38] in prisoner of war camps during World War II, allowed adequate distribution, and was considerably safer; this technique has been the recommended method of administration ever since. By contrast, quinidine is predictably hypotensive even with rate controlled infusions.

Quinine and quinidine both slow the rapid upstroke of the cardiac action potential by blocking the inward sodium current (I_{Na}), slowing depolarisation, and thereby widening the QRS complex.[2] This is the action of class 1 antiarrhythmic drugs. The cinchona alkaloids and related quinolines show little frequency dependence in this action, and so are classified as having class 1c activity. In common with other class 1 antiarrhythmic drugs, they are both negatively inotropic, although inhibition of I_{Na} does not correlate with the magnitude of negative inotropism. Both

	hERG K+ channel (I_{Kr}) IC_{50} (nmol/L)* A	*P falciparum* IC_{50} (nmol/L) B	Ratio A/B	Peak plasma concentration (nmol/L) C	Plasma protein binding (%) D	Ratio A/C
Xenopus oocyte system						
Quinine	57 000	110	518	50 000	90	1·1
Quinidine	4600	35	131	30 000	80	0·15
Chloroquine	8400	35	240	600	55	14
Embryonic kidney cell (HEK293) system						
Chloroquine	2500	35	71	600	55	4
Halofantrine	40	2	20	2200	83	0·02
Mefloquine	2600	7	455	4000	98	0·65
Lumefantrine	8100	15	540	6000	99	1·4
Artesunate/DHA	..	0·25	..	6000	93	..

hERG=human ether-a-go-go-related gene. I_{Kr}=rapidly activating inward potassium ion current. IC_{50}=50% inhibitory concentration. DHA=dihydroartemisinin. ..=not reported. *Direct comparisons cannot be made between hERG K+ channel IC_{50} nmol/L estimates obtained with different systems or between experiments that use different conditions. Although IC_{50} values representing 50% inhibition are mathematically robust, concentrations of free drug causing blockade of only 10–20% of the I_{Kr} function can be associated with TdP (torsades de pointes).

Table 2: **A comparison of activities of cardioactive antimalarial drugs on the hERG (I_{Kr}) channel, and against malaria parasites, and peak plasma concentrations in antimalarial treatment**

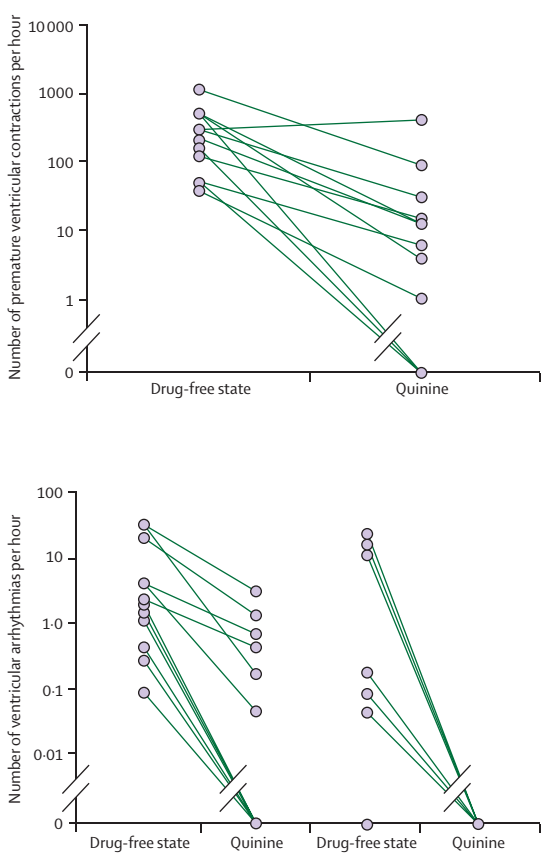

Figure 2: **The antiarrhythmic effects of quinine on premature ventricular contractions and ventricular tachycardia**
Adapted from Sheldon et al[47] with permission.

quinine and quinidine inhibit several different potassium channels.[39] They inhibit the mitochondrial ATP-regulated potassium channel via the sulphonylurea receptor,[40] and both quinine and quinidine are also potent stimulants to pancreatic β-cell insulin secretion[41,42] by inhibiting this channel.[43]

For inhibition of the hERG (I_{Kr}) channel, quinidine and quinine have very different activities (table 2). For example, the 50% inhibitory concentration (IC_{50}) values in xenopus oocytes were 4·6 µmol/L for quinidine and 57 µmol/L for quinine.[44,45] Although free plasma-drug concentrations in vivo might not be directly comparable, relative activities are probably preserved. Since free concentrations of the two drugs are similar in the treatment of malaria, this large difference in effects on the hERG channel explains why quinine has very little effect on ventricular repolarisation in vivo. QT prolongation with quinine is about four times less than with quinidine[46] and results mainly from prolongation of the QRS interval with little JTc prolongation.[47] Quinine is thus antiarrhythmic (figure 2). Quinine and quinidine are approximately equipotent in blocking the L-type calcium channel,[48] and both cause weak vagal inhibition.

No significant cardiotoxicity has been reported in large prospective studies of quinine both in uncomplicated and severe falciparum malaria, with total plasma concentrations up to 20 µg/mL (free concentrations up to 2 µg/mL or 6·2 µmol/L).[49–52] Indeed, the paucity of arrhythmias in this severe infection (in which myocardial sequestration is prominent) could be because of quinine's antiarrhythmic action. By contrast, at comparable concentrations of free drug quinidine is predictably hypotensive and causes marked QT prolongation.[53] Although arrhythmias occur very rarely in severe malaria, there is no convincing evidence that the few that do occur result from quinine. QT prolongation by more than 25% occurs in less than 10% of patients receiving high dose intravenous quinine.[49,54] Slight widening of QRS interval is usual, and is more pronounced in young children (mean 17%).[55] There have been occasional reports of apparent cardiotoxicity after quinine administration in elderly white patients with severe malaria. The difficulty in interpreting iatrogenic causation is that severe falciparum malaria is a multisystem disease, and, as the probability of death declines the longer the patient survives, death is most common in the hours after admission to hospital. That some patients will die during or shortly after starting treatment is not surprising. Disentangling the lethal disease processes, especially in elderly individuals with pre-existing cardiovascular disease, from any iatrogenic toxicity is very difficult. But the very large body of safety data from younger and fitter patients treated with quinine for severe malaria does suggest that if significant cardiotoxicity from quinine (conduction disturbances, dysrhythmias, hypotension) when given by rate controlled infusion does occur at all in the normal context of use, then it is very unusual. Quinidine, by contrast, commonly causes hypotension when given by

rate controlled intravenous infusion and predictably prolongs the QT interval with marked JT prolongation (table 3).[53] Quinidine is therefore potentially dangerous, and needs careful monitoring when given intravenously. Hypotension should be treated with saline or volume expanders.

Chloroquine

Chloroquine rarely causes conduction disturbances[56] and cardiomyopathy in chronic use in rheumatic diseases. Chloroquine in overdose (as in self-poisoning or when given by rapid intravenous injection) is certainly cardiotoxic and potentially lethal.[57–61] In some countries, chloroquine is an important cause of death from self-poisoning. Hypotension is common in self-poisoning; both tachycardias and bradycardia with atrioventricular block can occur, and there is consistent intraventricular conduction delay (widening of the QRS interval). Both peripheral vasodilatation and chloroquine's negatively inotropic effect contribute to shock. In the intensive care unit, cardiac arrest can follow intravenous thiopentone administration to patients poisoned with chloroquine.[58] Diazepam had been suggested to be an antidote, but recent studies do not support a specific role for this drug above good haemodynamic and ventilatory support.[58–61] As with the cinchona alkaloids, lethal hypotension can follow intravenous injection (table 3). Cardiovascular toxicity, and in particular hypotension, was the probable cause of sudden death that sometimes followed parenteral chloroquine administration for the treatment of malaria in children, and led WHO to recommend that its parenteral use should be discontinued in 1984.[62] Pharmacokinetic assessments with compartmental modelling provided an explanation for this event. These studies showed that chloroquine had a very small volume of the central compartment by comparison with its very large total apparent volume of distribution.[63–65] Because the drug was absorbed very rapidly following intramuscular and also subcutaneous injection, transiently toxic peak concentrations occurred. This occurrence was circumvented simply by giving the drug either by continuous rate controlled infusion, or by splitting intramuscular or subcutaneous injections and giving them every 4–6 h.[64,65] There is no evidence for clinical cardiotoxicity after oral administration of antimalarial treatment doses (table 4). In detailed pharmacokinetic-pharmacodynamic assessments after intravenous administration, only slight prolongation of the QRS interval (about 12%) was seen with T wave flattening but no changes in the QT interval. Slight QTc prolongation and T wave flattening were noted in a study of three adults who received 100 mg oral chloroquine (base) daily.[66]

The largest and most detailed study of the effects of chloroquine on the QT interval was a study comparing chloroquine and a new aminoquinoline compound AQ-13. 4 h after receiving 600 mg chloroquine (base equivalent), adult volunteers had a mean 16 ms (95% CI 9–23) prolongation of the Bazett corrected QT interval. Following the second dose of 600 mg, mean prolongation was 12 ms (18–38). As with many drugs, the effects on the QT interval were greater in women. QRS and JT interval prolongation was not distinguished in this study.[67]

Chloroquine hypotension results from both arteriolar dilatation and venodilatation, as a result of alpha blockade and mechanisms involving nitric oxide and histamine release.[68] Chloroquine is negatively inotropic at low micromolar concentrations.[69,70] In laboratory electrophysiological studies at low micromolar concentrations chloroquine lengthened the action potentials of cat Purkinje fibres, and increased automaticity.[71,72] Chloroquine blocked the inward sodium current, I_{Na} (the class 1 effect), the L-type calcium current (I_{Ca}-L), and two potassium currents: I_{K1} and the rapid delayed rectifier outward currents (I_{Kr}; the hERG channel).[10,72,73] These findings explain the prolongation and reduction in maximum velocity (*V*max) of cardiac action potentials. The mean chloroquine IC_{50} value for hERG channel inhibition in xenopus oocytes was 8·4 μmol/L,[10] which is high by comparison with its antiparasitic activity, and suggests that

	Hypotension if injected rapidly	Hypotensive with rate controlled infusion	ECG QRS widening	ECG QT prolongation
Quinine*	+++	0	+	+
Quinidine*	+++	++	+	+++
Chloroquine*	+++	0	+	+/–
Artesunate	0	0	0	0

ECG=electrocardiogram. 0=none. +/–=borderline. +=slight. ++=moderate. +++=severe. *Potentially lethal if given by intravenous injection.

Table 3: **Cardiovascular effects of intravenously administered antimalarial drugs**

	Conduction abnormalities reported	ECG QRS widening	ECG QT prolongation	Cardiovascular toxicity in overdose
Quinine	+	+	+	++
Quinidine	+	+	+++	+++
Chloroquine	+	+	+/–	+++
Amodiaquine	+/–	+/–	+/–	..
Mefloquine	+	0	0	..
Halofantrine	++	+	+++	..
Lumefantrine	0	0	0	..
Piperaquine	0	+	0	..
Primaquine	..	..	..	..
Pyrimethamine	0	0	0	0
(Chlor)proguanil	0	0	0	0
Atovaquone	0	0	0	0
Dihydroartemisinin*	0	0	0	0

ECG=electrocardiogram. ..=no data. 0=none. +/–=borderline. +=slight. ++=moderate. +++=severe. *Dihydroartemisinin is the active metbolite of artesunate and artemether.

Table 4: **Cardiovascular effects of orally administered antimalarial drugs**

only very high concentrations in vivo might cause clinically significant QT prolongation (table 2). Taken together these data indicate that chloroquine does not have significant cardiovascular toxicity if given in the correct doses and intravenously at the correct rate, but that the therapeutic ratio is narrow, and significant electrophysiological effects do occur at plasma concentrations approaching the micromolar range.

Amodiaquine

There are very few data on amodiaquine, or the related intramuscular preparation amopyraquine; there has only been one recent study of amodiaquine in which slight prolongation of PR, QRS, and QTc was noted.[73] These changes were considered clinically insignificant. Furthermore, they did not correlate with plasma concentrations of either amodiaquine or desethyl amodiaquine (the main metabolite), which suggests they might have been related to disease rather than drug. Most of the quinoline derivatives were introduced into medicine before modern techniques of cardiotoxicity investigation were introduced. Several new 4-aminoquinoline molecules are under development, including N-tertiary-butyl-isoquine, an amodiaquine analogue. Cardiotoxicity studies in the preclinical development of these molecules will provide useful information both on the new and the older comparator drugs. More information is needed on the safety profile of amodiaquine, since it is an increasingly used drug.

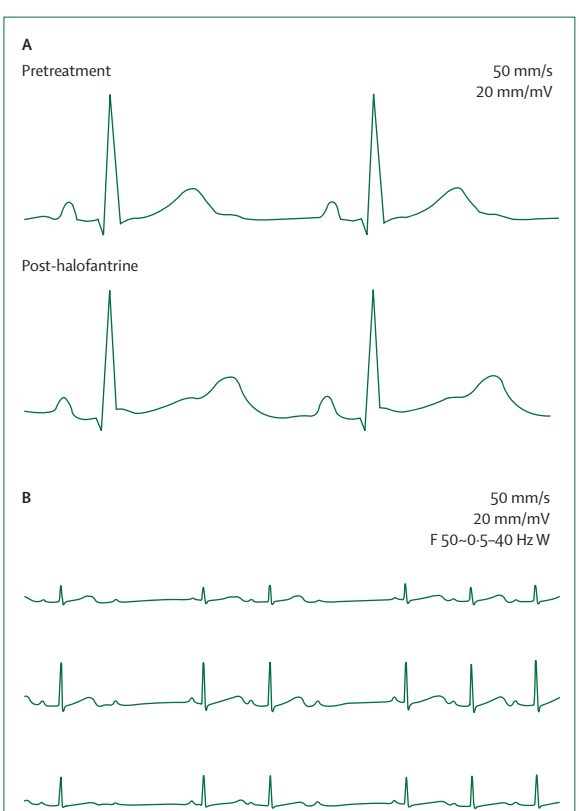

***Figure 3*: The effects of halofantrine on cardiac conduction in the treatment of malaria**
(A) Prolongation of the electrocardiograph QT interval. (B) Atrioventricular block: the Wenckebach phenomenon.

Mefloquine

There is no convincing evidence for significant cardiotoxicity following mefloquine administration,[74,75] despite initial reports that suggested mefloquine might cause significant bradycardia and hypotension, and very occasional case reports of cardiac dysrhythmias in people with pre-existing heart disease.[76] Sinus bradycardia does occur in some recipients of mefloquine, but is very seldom severe. Gap junctions are aggregates of cell–cell channels composed of connexins and these mediate direct intercellular diffusion of cytoplasmic ions, small metabolites, and signalling molecules. In the mouse heart the cell to cell conductance through one connexin (of the 20 identified) that is particularly abundant in the sinoatrial and atrioventricular nodes is blocked by mefloquine (IC_{50} 10 µmol/L), which could be relevant to the development of bradycardia.[77]

In experimental models, mefloquine is negatively inotropic, probably by blockade of L-type calcium channels,[78] but there is no evidence for significant negatively inotropic effects in the treatment of malaria. Mefloquine inhibits the slow delayed rectifier potassium channel (I_{Ks}; KvQT1/minK), but is a weak inhibitor of the hERG potassium channel. In studies of wild-type hERG channels in stably transfected human embryonic kidney cells (HEK293) the IC_{50} was similar to chloroquine (chloroquine 2·5 µmol/L, mefloquine 2·6 µmol/L) but 60 times higher than for halofantrine. In stably transfected chinese hamster ovary (CHO) cells, the hERG channel IC_{50} was 5·6 µmol/L.[78–80] Clinical and electrocardiographic studies have suggested either no or slight prolongation of the QT interval. Apart from mild sinus bradycardia there is no convincing evidence that mefloquine causes arrhythmias in the treatment of malaria.[81,82] Interaction studies with quinine do not suggest synergistic toxicity,[83] although in one small volunteer study there was greater QTc prolongation with the two drugs combined than when given individually.[84] These data are generally reassuring with the caveat that, with halofantrine, there is a potentially dangerous interaction.[3] Further interaction studies with other drugs that block the hERG channel are needed.

Halofantrine

Halofantrine is metabolised in vivo to desbutyl halofantrine, which is also biologically active. Halofantrine induces marked QT prolongation at therapeutic concentrations,[3,82,85–88] and is associated with sudden death, presumably from malignant ventricular tachyarrhythmias (table 4).[3,88] Halofantrine also prolongs the PR interval and can cause transient heart block at higher plasma concentrations[3] (figure 3). The absorption of this lipophilic antimalarial drug is very variable and

depends on coadministration with fats. Thus, the plasma concentrations vary considerably between individuals. Because cardiotoxicity is concentration dependent,[3,82,85–96] the cardiotoxic potential of halofantrine in an individual is unpredictable. Halofantrine and desbutyl halofantrine are both very potent inhibitors of the hERG potassium channel (table 2) and readily produce TdP in experimental models.[78,86–96] Given that there are now several equally effective and much safer alternatives, halofantrine should not be used as an antimalarial drug.

Although mefloquine alone has little effect on ventricular repolorisation, it markedly exacerbates QT prolongation caused by halofantrine.[3,97] The synergy of mefloquine with halofantrine in prolonging the QT interval is probably explained by its inhibition of the slow delayed rectifier potassium channel (I_{Ks}; KvQT1/minK).[79]

Lumefantrine

By contrast with halofantrine, lumefantrine is a very weak antagonist of the hERG cardiac potassium channel.[77] The drug has been assessed extensively and does not produce significant adverse cardiac effects in vivo, and has no significant effects on electrocardiograph.[98–100] In an overview of different trials, 6% of 291 children receiving the six-dose regimen of artemether-lumefantrine had a QT prolongation of longer than 60 ms (Fridericia's correction).[34] In a large prospective assessment in Thailand there was no correlation between plasma concentrations of lumefantrine, over a 1000-fold range, and changes in electrocardiographic indices.[99] These studies indicate that lumefantrine has no significant cardiovascular toxicity.

Primaquine

The cardiovascular activity of the 8-aminoquinoline primaquine has not been studied extensively. Primaquine blocks the inward sodium current I_{Na}, slowing the upstroke of the action potential,[101,102] so like many of the quinolines, it does have class 1 activity. Limited available evidence does not suggest significant cardiovascular toxicity.

Pyrimethamine-sulfadoxine

There is no evidence either from human or experimental animal studies that pyrimethamine, antimalarial biguanides, sulphones, or sulphonamides are directly cardiotoxic.[103]

Atovaquone-proguanil

There is no evidence from clinical or laboratory studies that atovaquone, proguanil, or its biologically active metabolite cycloguanil, have significant cardiovascular toxicity in therapeutic use.[104]

Artemisinin and derivatives

These potent antimalarial drugs are remarkably well tolerated in therapeutic use. Artemisinin has now largely given way to the derivatives of the more potent dihydroartemisinin, artesunate, artemether, and artemotil. These are metabolised in vivo back to dihydroartemisinin. In clinical trials there have been no adverse cardiovascular effects noted in thousands of severe malaria patients and tens of thousands of uncomplicated malaria patients treated with these drugs. In animal models, the oil-based derivatives artemether and arteether (artemotil) given intramuscularly in high doses produce an unusual selective pattern of damage to brain stem nuclei, particularly those involved with hearing and balance.[105,106] When the same drugs are given orally or water-soluble drugs are given, neurotoxicity requires considerably larger doses,[107–109] suggesting that neurotoxicity results from sustained CNS exposure to toxic concentrations. Thus the pharmacokinetic properties of the drugs determine their neurotoxic potential. Where neurotoxicity was shown in beagle dogs and rats, prolongation of the QT interval was also noted.[105–107] However, because neurotoxicity was coincident with cardiotoxicity, it was not clear whether these effects represented direct cardiotoxicity, or were an indirect result of central nervous system toxicity. Neurotoxicity has not been found in human beings. Nonetheless, these findings, and confusion between disease and possible drug-related effects, have left uncertainty over the cardiotoxic potential of this class of drugs.

In the isolated guineapig heart, millimolar concentrations of artesunate are negatively inotropic,[110] whereas nanomolar concentrations are antimalarial. Intravenously injected doses about 300 times higher than those used clinically were hypotensive in the rabbit, but doses below 160 mg/kg (human dose 2·4 mg/kg) in the dog had no effect on the electrocardiograph,[111] suggesting a very wide therapeutic ratio. In guineapig myocytes, artemisinin (50 µmol/L) blocked the two components of delayed outward rectifier potassium ion current (I_K), the rapidly activating inward potassium ion current (I_{Kr}), and the slowly rectifying outward potassium ion current (I_{Ks}).[112] There are no reported electrophysiological data on artesunate, artemether, or dihydroartemisinin. In a large randomised comparison of high-dose artemether and quinine in adults with severe malaria, serial electrocardiographs were recorded in 301 patients; slight QT prolongation was noted in both groups, 11 of 152 (7%) artemether recipients and 12 of 133 (9%) quinine recipients had an increase of more than 25%,[49] but the contributions of drug and disease cannot be determined. In another comparative trial one of 31 patients with severe malaria treated with artemether had transient right bundle branch block, six had non-specific T-wave changes and two had QT prolongation (both had sinus bradycardia).[113] There were no dysrhythmias or adverse cardiovascular effects in either study. However, when artemether is given orally to healthy individuals, despite plasma concentrations of artemether and dihydroartemisinin that were up to ten times higher than followed intramuscular administration, no electrocardiographic changes were seen.[114]

Rapid intravenous administration of artesunate is not associated with cardiovascular effects despite transiently

Search strategy and selection criteria

Data for this Review were identified by searches of Medline, Current Contents, and references from relevant articles; search terms were the antimalarial drug names plus "cardiac", "myocyte", "electrocardiogram", "QT", "hERG", "toxicity", "poisoning", and "hypotension". English, French, and German language papers were reviewed. No date restrictions were set in the searches.

high plasma concentrations of artesunate and dihydroartemisinin. These concentrations are up to two orders of magnitude higher than with intramuscular artemether.[115] This lack of relation with drug concentration suggests that the QT interval prolongation noted in experimental animals might have been caused by central nervous system toxicity. Price and colleagues[22] studied 216 patients who received various oral artemisinin containing regimens; 1 h after taking the artemisinin derivative there was a very small (3·5%) decrease in mean heart rate, a small increase in the PR interval (5·3%), and a very small decrease in the Bazett's rate corrected QT interval (0·7%). In other studies with artemether and the other oral artemisinin derivatives in uncomplicated malaria, including those with artemether-lumefantrine mentioned previously,[34,99,100,116] there was no significant QT prolongation, and no other significant electrocardiographic abnormalities were noted despite much higher plasma concentrations of both artemether and dihydroartemisinin than follow intramuscular artemether. Taken together, these observations suggest the artemisinin derivatives do not have any significant cardiovascular toxicity.

Conclusion

Several of the quinoline antimalarial drugs are vasodilators and affect myocardial depolarisation (class 1 effect), but only quinidine and halofantrine produce clinically significant prolongation of ventricular repolarisation (class 3 effect). The other classes of antimalarial drugs (artemisinins, antifols, atovaquone) do not have significant cardiovascular effects. Recovery from malaria is associated with significant lengthening of the electrocardiograph QT interval that has sometimes mistakenly been ascribed to the antimalarial drug treatment.

Conflicts of interest

I am Chairman of the WHO malaria case management technical expert group.

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