THE EFFECT OF QUININE ON QT INTERVAL IN PATIENTS IN A TERTIARY CARE HOSPITAL

Mohammad Humayun[1], Iqbal Haider[2], Aliena Badshah[3]

ABSTRACT

Objectives: *To determine the frequency of patients developing QT prolongation with the use of intravenous (IV) quinine therapy in medical unit D of Khyber Teaching Hospital, Peshawar.*

Methodology: *This cross-sectional study was conducted in Medical unit D of Khyber Teaching Hospital, Peshawar, from 1st June, 2011 to 30th November, 2011. The study population comprised of male and female patients who tested positive for malarial parasite on peripheral blood smear. Treatment was started with intravenous quinine for a minimum duration of 3 days to a maximum duration of 5 days. Electrocardiography (ECG) was done before starting the patients on IV quinine therapy and QT interval was calculated. Repeat ECG was done 72 hours after starting the therapy. Patients were evaluated for prolongation of the QT interval after initiation of treatment with quinine. All the statistical analyses were done using statistical program SPSS version 17.0. The mean with standard deviation, frequency and percentages were reported. Significance was tested at $p<0.05$.*

Results: *Out of a total of 200 patients, only 2 female patients (1%) had a prolongation of the QT interval from their normal baseline interval before treatment. It appears that the cardiotoxic effects of quinine have been overstated and that the risk of QT prolongation and fatal arrhythmias is minimal with quinine therapy.*

Conclusions: *It can thus be concluded that quinine is a safe drug for the treatment of malaria with negligible cardiotoxic adverse effect profile.*

Key Words: *Quinine, Electrocardiography (ECG), QT interval, Arrhythmias, Cardiotoxic adverse effect*

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INTRODUCTION

Malaria is an important cause of illness and death in children and adults in tropical countries. Worldwide, in 2006, an estimated 247 million (189-327 million) malaria cases occurred, with an approximated 881,000 (610,000-1,212,000) deaths[2]. There are nearly 500 million clinical cases of malaria worldwide each year and 1.1 to 2.7 million people die annually[2]. Plasmodium falciparum is the species that can cause severe, complicated malaria and death. Antimalarial drug resistance is now generally acknowledged to be one of the greatest threats to our ability to 'roll back malaria'. Quinine is the drug of choice for plasmodium falciparum but sporadic cases of resistant strains are being reported with monotherapy[3,4]. Artemisinin derivatives are presently effective but are costly for a developing country to be used on a mass scale[5]. Intravenous (IV) quinine (a 4-quinoline methanol) has been the mainstay of treatment for such severe malaria.

Cardiac toxicity has been a major concern with the use of IV quinine or quinidine, with quinidine considered to be more toxic than quinine[4,6]. The primary mechanism of cardiotoxicity caused by quinine or quinidine is the prolongation of the electrocardiographic (ECG) QT interval which can cause potentially fatal ventricular arrhythmias, including torsades de pointes, and even sudden death.

[1-3] Department of Medicine, Khyber Teaching Hospital, Peshawar - Pakistan

Address for Correspondence:
Dr. Iqbal Haider,
Department of Medicine,
Khyber Teaching Hospital, Peshawar - Pakistan
E-mail: driqbalhaider@yahoo.com

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Intravenous (IV) quinine (a 4-quinoline methanol) has been the mainstay of treatment for severe falciparum malaria, although in some countries, including the United States, quinidine, the dextrorotatory diastereoisomer of quinine, is used because of the non-availability of IV quinine[2].

Since the 1960s, chloroquine-resistant and multidrug-resistant strains of plasmodium falciparum have emerged in Africa and Southeast Asia and have spread worldwide[3]. Newer anti-malarial drugs were developed including mefloquine and halofantrine. Because both drugs are administered orally, their widespread use was anticipated for the treatment of uncomplicated cases of drug-resistant plasmodium falciparum infection. However, in 1993, reports of severe and sometimes fatal cardiotoxicity associated with the use of halofantrine led the World Health Organization to limit its use[8], and as of 2002, there were at least 20 reports of fatal cardiac complications relating to use of the drug[9]. These events were attributed to a QT prolongation effect of halofantrine, identified in several human studies of the drug[10,11]. These unexpected cardiac problems resulted in the withdrawal of the drug from the market in many countries including Pakistan but excluding parts of West and Central Africa[12]. These facts underline the importance of examining the cardiotoxic potential of quinoline and other structurally related anti-malarial drugs before the wider marketing of newer drugs.

Quinine acts primarily as a blood scizonticide; it has little effect on sporozoites or pre-erythrocytic forms of malarial parasites. Though vivax malaria is treated with chloroquine and primaquine as the drug of choice for eradication of plasmodium vivax, quinine also is gametocidial for plasmodium vivax and erythrocytic forms of malarial parasite[13]. This is one reason why it is also used for treatment of vivax malaria especially in endemic areas. In part because it is a weak base, quinine concentrates in the acidic food vacuoles of plasmodium falciparum. The drug inhibits the non-enzymatic polymerization of the highly reactive, toxic heme molecule into a non-toxic polymer pigment called hemozoin. This is proposed to occur by a two-step process whereby the quinoline binds first to heme, and the resulting heme-drug complex binds to and saturates the heme-polymer chains. Whether consequent buildup of heme itself, heme-quinoline complexes, or both kill the parasites, is not established[14].

As noted earlier, cardiac toxicity has been a major concern with the use of IV quinine or quinidine, with quinidine considered to be more toxic than quinine[4,6]. In 1966, Francois Dessertenne described a specific electrocardiographic form of polymorphic ventricular tachycardia, which he termed "torsades de pointes" (TdP)[15,16]. In the seminal article, Dessertenne made no attempt to suggest the mechanism of TdP and, until recently, there has been considerable conjecture as to the pathophysiology of this arrhythmia. Since the original work by Dessertenne, it has been well recognised that many conditions may cause prolonged or abnormal repolarisation (that is, QT interval prolongation and/or abnormal T or T/U wave morphology), which is associated with TdP [17]. If TdP is rapid or prolonged, it can lead to ventricular fibrillation and sudden cardiac death. Essentially, TdP may be caused by either congenital or acquired long QT syndrome (LQTS). Many of the drugs that were initially known to prolong the QT interval were antiarrhythmics, and quinidine was the most commonly implicated agent. Surprisingly, many non-cardiac drugs have also been reported to cause QT prolongation and/or TdP recently. In a survey in both the UK and Italy, non-cardiac drugs that have pro-arrhythmic potential (that is, have an official warning on QT prolongation or TdP, or with published data on QT prolongation, ventricular tachycardia, or class III effect) alone represented 3% and 2% of total prescriptions in both countries, respectively[15]. The danger of drug induced pro-arrhythmia is therefore serious.

In our study, the effect on the QT interval of quinine was studied in patients in our tertiary care hospitals where patients with smear positive for plasmodium falciparum and plasmodium vivax are being treated with quinine and doxycycline. The aim of this study was to clarify whether the results obtained from this model could be used to predict the cardiotoxicity of quinine when used in clinical settings. In this study side effect profile of treatment was tolerable and in negligible number of patients did it warrant stopping therapy.

METHODOLOGY

This descriptive study was carried out at the Department of Medicine, Khyber Teaching Hospital, Peshawar - Pakistan, from 1st June 2011 to 30th November 2011. A well written informed consent was obtained either from patient or close relative in case of unconscious patients. The study population comprised of patients of both gender,

aged 12 years and above, presenting with high grade fever, positive thick and thin peripheral blood films for malarial parasites and who had not taken any anti-malarial treatment in the preceding 7 days. Patients presenting with high grade fever but without peripheral blood smear evidence of malarial parasites or otherwise labeled as having pyrexia of undetermined origin (PUO) were excluded from the study. After carefully fulfilling the inclusion and exclusion criteria, patients were admitted to the hospital to ensure compliance. A detailed history was taken and physical examination performed and all the information was recorded in a well designed questionnaire. Blood samples were taken for routine hematology and biochemistry analysis which included complete blood count, platelet count, blood glucose fasting and random levels, serum urea and creatinine levels, urine for routine examination and microscopy, and serum for liver function tests and electrolytes. Treatment was started with slow intravenous quinine infusion at a dose of 10mg of salt/kg body weight 8 hourly for a minimum duration of 3 days to a maximum duration of 5 days. Oral acetaminophen 1 gm 4 hourly was given for a temperature of > 101°F. Vital signs were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. Electrocardiography was done before starting the patients on IV quinine therapy and QT interval was calculated. Corrected QT interval (QT_c) was calculated using Bazett's formula[7]:

$$QT_C\ (s) = QT\ interval / \sqrt{}\ RR\ interval$$

Normal range for corrected QT interval (QT_c) was taken as 0.35-0.44sec.

The patients were examined twice daily for any adverse effects of the drugs or for the development of any complications of the disease. Repeat ECG was done 72 hours after starting the therapy. Tolerability outcome measure was the development of treatment related adverse effects resulting in discontinuation from the study. All the statistical analyses were done using statistical program SPSS version 17.0. The mean with standard deviation, frequency and percentages were reported. Significance was tested at $p<0.05$.

RESULTS

A total of 200 patients aged between 12-90 years were included in the study, amongst them 143 (71.5%) were male and 57 (28.5%) were female.

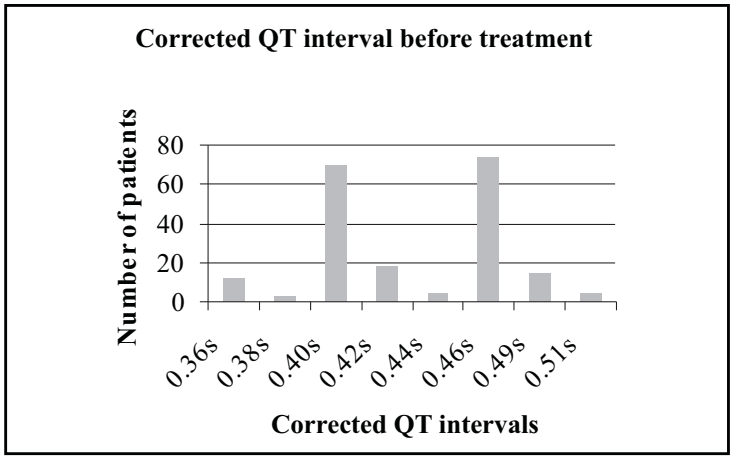
The means and standard deviations of age and electrocardiographic parameters are given in Table 1.

Patients were tested positive for malarial parasite, with 116 (58%) patients showing positivity for plasmodium vivax and 84 (42%) patients showing positivity for plasmodium falciparum. Patients had a QT_c ranging from 0.36s to 0.51s before the start of quinine therapy (Graph 1). Following quinine therapy, 2 female patients were noticed to have their QT_c prolonged from the baseline QT_c before treatment (Graph 2). Of these 2 patients, one who was plasmodium vivax positive had a QT_c of 0.42s before initiation of IV quinine therapy. Three days following treatment with quinine, the repeat ECG showed a prolonged QT_c of 0.6s. The second patient had been started on IV quinine after being labeled as Falciparum malaria at Emergency unit. Her QT_c before quinine therapy was 0.46s, while repeat ECG after 3 days of treatment showed a QT_c of 0.49s. The first patient expired on the 4th day of admission despite withholding quinine therapy, while the second patient stayed asymptomatic even before the cessation of quinine therapy. Thus the overall frequency of QT interval prolongation among patients admitted to our medical unit was 1%.

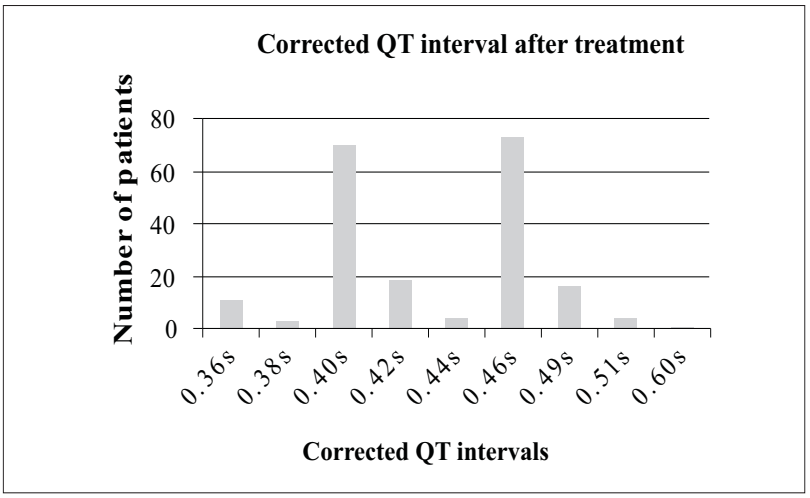
Table 1: Mean and Standard deviations of age and electrocardiographic parameters

Parameter	Mean	Standard Deviation
Age	46 years	1.5
QT interval before treatment with quinine	0.36sec	0.0028
Corrected QT interval before treatment with quinine	0.45sec	0.0021
QT interval after treatment with quinine	0.38sec	0.0007
Corrected QT interval after treatment with quinine	0.46sec	0.0014

Graph 1: QT_c Ranging from 0.36s to 0.51s before the start of Quinine therapy



Graph 2: QT_c Prolonged from the baseline QT_c before treatment



DISCUSSION

In our study, out of a total of 200 patients, only 2 female patients (1%) were observed to have prolonged QT interval. Of these 2 patients, one who was plasmodium vivax positive, had a QT interval of 0.38s (QT_c=0.42s) before initiation of IV quinine therapy. Three days following treatment with quinine, the repeat ECG showed a prolonged QT interval of 0.48s (QT_c=0.6s). The quinine therapy was with held and was replaced with artemether combination drug and ultimately patient expired in intensive care on 5th day of admission due to concomittent DIC. The second patient's peripheral smear documented falciparum trophozoites was started on IV quinine. QT interval before quinine therapy was 0.36s (QT_c=0.46s), while repeat ECG after 3 days of treatment showed a QT interval of 0.44s (QT_c=0.49s). However, the patient had not developed any alarming symptoms.

The risk of QT interval prolongation with quinine in our study (1%) is negligible as compared to a risk of 21% in another study in Thai children[18]. A controlled trial of quinine and artemether was conducted in Vietnamese adults with severe falciparum malaria[19]. Results of the study showed that there were no significant electrocardiographic abnormalities in the patients in whom recordings were made, although in 60 of the quinine recipients (45%), as compared with 38 of the artemether recipients (25%), the corrected QT interval was prolonged by more than 0.5

second (relative risk, 1.8; 95% confidence interval, 1.3 to 2.5; P=0.001). Only 12 patients in the quinine group (9%) and 11 in the artemether group (7%) had a corrected QT interval that was prolonged by more than 25% (P=0.67). Prolongation of the corrected QT interval was not associated with any other clinical finding, including the development of shock or the duration of coma. Other factors may have been implicated in the setting of such studies, thereby leading to significant cardiotoxic profile of the drug.

The findings of our study are comparable with those of another study conducted in Combined Military Hospital, Quetta, Pakistan, where QT prolongation was observed in 0.89% of the patients receiving I.V quinine[20]. Quinine is not recommended for use with other drugs known to cause QT prolongation, including Class IA antiarrhythmic agents (e.g., quinidine, procainamide, disopyramide), and Class III antiarrhythmic agents (e.g., amiodarone, sotalol, dofetilide). The use of macrolide antibiotics such as erythromycin should be avoided in patients receiving quinine. Fatal torsades de pointe was reported in an elderly patient who received concomitant quinine, erythromycin, and dopamine[21]. Although a causal relationship between a specific drug and the arrhythmia was not established in this case, erythromycin is a CYP3A4 inhibitor and could potentially increase quinine plasma levels when used concomitantly. A related macrolide antibiotic, troleandomycin, has been shown to increase quinine exposure in a pharmacokinetic study[21].

It appears that the individual cardiotoxic adverse effect of quinine has been over-exaggerated, and that the true incidence of life-threatening cardiac events is much less than usually hypothesized. Quinine cardiotoxicity may be significant in individuals who have congenital QT prolongation or who may be using other drugs side by side[3]. Apparently, the high levels of plasma alpha 1 – acid glycoproteins produced in severe malaria prevent quinine toxicity by binding the drug, thereby reducing the free fraction of quinine from about 15% down to 5% to 10% of its total concentration in plasma. As patients improve, levels of alpha 1 – acid glycoprotein decrease, the apparent volume of distribution expands, the systemic clearance increases, and the plasma levels of quinine fall[22]. There is no accumulation of the drug in the body upon continued administration, because their metabolites are excreted in the urine[23]. Quinine-related cardiac toxicity can occur at therapeutic or even sub-therapeutic plasma concentrations. It appears that the effect of quinine on the heart is cumulative rather than dose-related[24]. All the intravenous quinine candidates fall in this category[25]. Cinchonism, hypoglycemia and hypotension, on the other hand, are dose-related adverse effects of quinine therapy[13].

Quinine has been reported to have a low unbound fraction in plasma[17]. When assessing cardiotoxicity in human therapies, the possibility of finding differences in unbound fractions of an anti-malarial drug should also be considered. For example, the plasma unbound fraction of quinine was reported to be lower in cerebral malaria than in uncomplicated malaria[26], which may explain why severe quinine toxicity is unusual in severe falciparum malaria[27]. Moreover, large scale studies are needed to investigate the various factors that could influence the total concentration and consequently the unbound concentration of an anti-malarial drug to ensure safer use of drugs.

CONCLUSION

It has been well recognized that a prolonged QT interval (congenital or acquired) on the surface ECG is associated with an increased risk of TdP and/or sudden death. By far the most common cause of acquired long QT syndrome is drug induced, with anti-malarials being one of the most commonly implicated drug group. The results of our study reveal that the risk of QT interval prolongation with quinine is minimal, and it can be safely used for the treatment of malaria especially in malaria endemic areas where the parasite has acquired resistance to many conventional drugs. The risk of TdP associated with prolonged QT interval is still likely to remain a significant problem in the future. All physicians, pharmacists and patients who receive these drugs, should be made aware of this risk and educated accordingly, and take precautions to minimize pro-arrhythmia. Preclinical and clinical evaluations remain the cornerstone for assessing the arrhythmogenic potential of any new drug before approval.

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CONTRIBUTORS

MH conceived the idea, planned and supervised the study. IH & AB did the data collection, analyzed the study & wrote the manuscript. All the authors contributed significantly to the research that resulted in the submitted manuscript.