

Quinine-induced Arrhythmia in a Patient with Severe Malaria

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ABSTRACT

It was reported that there was a case of severe malaria patient with jaundice who presented with arrhythmia (premature ventricular contraction) while getting quinine infusion was reported. A man, 25 years old, was admitted to hospital with high fever, chill, vomiting, jaundice. The patient was fully conscious, blood pressure 120/ 80 mmHg, pulse rate 100 x/ minute, regular. On admission, laboratory examination showed Plasmodium falciparum (++++), total bilirubin 8.25 mg/dL, conjugated bilirubin 4.36 mg/dL, unconjugated bilirubin 3.89 mg/dL, potassium 3.52 meq/L. Patient was diagnosed as severe malaria with jaundice and got quinine infusion in dextrose 5 % 500 mg/8 hour. On the second day the patient had vomitus, diarrhea, tinnitus, loss of hearing. After 30 hours of quinine infusion the patient felt palpitation and electrocardiography (ECG) recording showed premature ventricular contraction (PVC) > 5 x/ minute, trigemini, constant type – sinoatrial block, positive U wave. He was treated with lidocaine 50 mg intravenously followed by infusion 1500 mg in dextrose 5 %/ 24 hour and potassium aspartate tablet. Quinine infusion was discontinued and changed with sulfate quinine tablets. Three hours later the patient felt better, the frequency of PVC reduced to 4 – 5 x/ minute and on the third day ECG was normal, potassium level was 3.34 meq/L. He was discharged on 7th day in good condition.

Quinine, like quinidine, is a chincona alkaloid that has anti-arrhythmic property, although it also pro-arrhythmic that can cause various arrhythmias, including severe arrhythmia such as multiple PVC. Administration of parenteral quinine must be done carefully and with good observation because of its pro-arrhythmic effect, especially in older patients who have heart diseases or patients with electrolyte disorder (hypokalemia) which frequently occurs due to vomiting and or diarrhea in malaria cases.

Key words : severe malaria, parenteral quinine, arrhythmia.

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INTRODUCTION

Malaria remains the most important parasitic infection in the world, especially in tropical and subtropical countries (accounting for 40% of world population) and is the leading cause of morbidity and mortality. It is estimated that approximately one billion malaria cases occur every year, resulting in 3 million deaths.¹ In malaria, mortality is due to complications in many vital organs.

Malaria with jaundice (total bilirubin level > 3 mg/dL) is one of the complications found in patients with severe malaria (based on the WHO criteria). Study by Wenas et al² at Bethesda Hospital, Tomohon, North Sulawesi (1990-1993) demonstrated that 46% of hospitalized patients with severe malaria were jaundiced. Data from Manado General Hospital in 1995, 1997 and 1998 demonstrated that the most common presentation of patients with severe malaria was malaria with jaundice (36.8%, 42.1%, 41.4% respectively), followed by cerebral malaria and malaria with acute renal failure.³ Our study in Samarinda, East Kalimantan found that 62.9% of patients with severe malaria were jaundiced.⁴ In Thailand, Harinasuta et al⁵ (1992) reported that 20 – 30% of hospitalized malaria patients were jaundiced.

Generally, the management of jaundiced patients is the same as that of patients with severe malaria with other complications, which is by using parenteral quinine or artemisinin derivatives (artemether or artesunate). The adverse effects of quinine are *chinconism syndrome* (tinnitus, temporary hearing loss, nausea, vomiting, dysphoria) that may occur at therapeutic levels (5–10 mg/L).⁶ Parenteral quinine may also cause hypoglycemia due to stimulation of insulin secretion, hypotension and arrhythmia.^{1,6} Rapid infusion of quinine can result in cardiovascular collapse (cardiogenic shock).^{6,7} Observation of infusion rate, blood pressure, heart rate, ECG, potassium level is very important during administration of quinine infusion.

Quinine-induced arrhythmia is rare; however, Hachfi et al and Algrain et al⁷ reported cases of arrhythmia

caused by quinine infusion. Bonington et al⁷ reported a fatal ventricular fibrillation case in a 71 year old woman without any history of heart disease who was given slow rate quinine infusion.

We report a case of a 25 year old man suffering from severe malaria with jaundice receiving quinine infusion who presented with arrhythmias during treatment (*premature ventricular contraction and sinoatrial block*).

CASE ILLUSTRATION

A man, 25 years of age, who lived in Bitung (North Sulawesi), was admitted to Manado General Hospital in December 1998 with a main complaint of fever. The patient suffered from high fever, and cold sweats 8 days prior to admission as well as headache, nausea, vomiting, loss of appetite, weakness, and right upper quadrant abdominal pain. Three days prior to admission patient realized that he had yellow eyes and passed dark-yellow urine. Patient had taken 3 tablets of sulfadoxine-pyrimethamine, was treated at a hospital in Bitung for one day, and then moved to Manado General Hospital. There was no history of malaria, typhoid, jaundice or hypertension, heart diseases, pulmonary diseases, kidney diseases. The patient lived and worked in Bitung, which is also an area with endemic malaria, and did not travel to other areas in the last year.

The patient was fully conscious, his general condition was good, body weight 58 kg, blood pressure 120/80 mm Hg, pulse rate 100x/minute, regular, respiratory rate 22x/minute, and body temperature 39.2°C. The sclera was jaundice and there was minor subconjunctival bleeding. Physical examination results of the heart and lungs were within normal limits. There was liver enlargement (3 cm below right costal margin) with sharp margin and pain on palpation; the spleen was not palpable. The extremities were normal.

On admission, laboratory examination demonstrated his hemoglobin 14.1 g/dL, WBC 10,200/iL, platelet 210,000/iL, ureum 27.3 mg/dL, creatinine 1.3 mg/dL, random blood sugar 119 mg/dL, SGOT 51 IU/L, SGPT 151 IU/L, total bilirubin 8.25 mg/dL, conjugated bilirubin 4.36 mg/dL, unconjugated bilirubin 3.89 mg/dL, sodium 138 meq/L, potassium 3.52 meq/L, chloride 102 meq/L, thick blood smear *Plasmodium falciparum* ++++.

Based on all the data above, the patient was diagnosed to have severe malaria with jaundice. The management of this patient was with 500 mg quinine dihydrochloride infusion in 500 ml dextrose 5% every

8 hours, injection of metoclopramide if necessary, and injection of vitamin K 10 mg per day.

On the second day, the patient's body temperature 38.8°C, and he had vomiting, tinnitus and loss of hearing, and a urine production of 1300 ml/ 24 hours. Malarial blood smear: *P. falciparum* ++, blood sugar 114 mg/dL. ECG demonstrated occasional *premature ventricular contraction (PVC)*. The heart and lungs were normal on chest X-ray. After 30 hours of quinine infusion, the patient felt nausea, dizzy, bloating, palpitation and had diarrhea 5 times. His abdomen was slightly distended, his bowel sound increased, his heart beat was irregular. ECG demonstrated PVC 4 times/minute. Subsequent ECG 2 hours later demonstrated a PVC of over 5times/minute, trigemini, constant type-sinoatrial block, positive U wave, QTc interval 0.32 seconds (see figure below). The diagnosis was severe malaria with arrhythmias. He was treated with lidocaine 50 mg intravenously followed by 1500 mg in 500 ml dextrose 5% 8 drops/minute and also attapulgit (Biodiar®) 3 x 2 tablets, potassium aspartate tablet (Renapar®) 3 x 1 because of diarrhea. Quinine infusion was stopped and was changed with sulfate quinine tablet 200 mg 3x2. Three hours later the PVC was 4–5 times/minute. The patient felt better, and the palpitation was reduced.

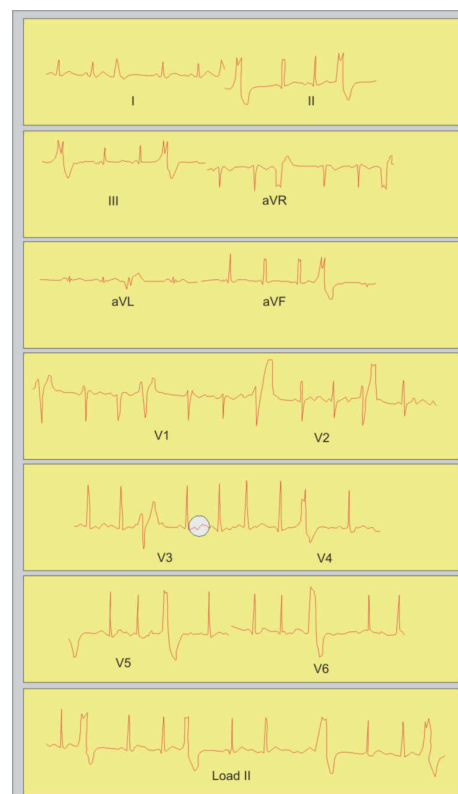


Figure 1.

On the third day, there was no fever and vomiting, but the patient had diarrhea (defecated 3 times). The patient's blood pressure was 120/70 mmHg, his pulse rate regular at 84x/minute, his body temperature 37°C, while jaundice was still positive. Laboratory findings were as follows: sodium 134 meq/L, potassium 3.34 meq/L, chloride 102 meq/L, random blood sugar 123 mg/dL, and malarial blood smear -. ECG was normal and lidocaine infusion was terminated after 24 hours.

On the fourth day, there was no fever, vomiting, or palpitation. The sodium level was 136 meq/L, potassium 3.44 meq/L, chloride 105 meq/L, malarial blood smear. Treatment was continued.

On the fifth day, the patient felt well, with a hemoglobin level of 13.6 g/dL, WBC 6,400/iL, platelet 164,000/iL, total bilirubin 2.48 mg/dL, conjugated bilirubin 1.26 mg/dL, unconjugated bilirubin 1.22 mg/dL, SGOT 32 IU/L, SGPT 71 IU/L, and malarial blood smear.

The patient was discharged on the 7th day without any complaints and in good general condition. The patient was given vitamins and was asked to come to the Infectious Diseases and Tropical Medicine Clinic in a week's time, but he did not show up.

DISCUSSION

Common clinical presentations of plasmodium infection are intermittent fever, shivering, sweaty, headache, and weakness. Approximately 20% of malaria patients present with vomiting and about 5% with diarrhea.¹ Anemia and spleen enlargement are usually found in malaria patients. Platelet count is usually low while WBC is normal in the majority of patients. In this case the patient had fever, cold, sweaty, weak, headache, vomiting, jaundice, diarrhea, and dark-yellow urine. Diarrhea might be caused by plasmodium infection although other causes were also possible. Physical examination of this patient revealed high fever, subconjunctival bleeding, jaundice, and liver enlargement. Laboratory examination demonstrated no anemia, normal platelet count, slightly increased WBC, increased SGOT and SGPT levels (51 IU/L and 151 IU/L respectively), elevated total bilirubin, conjugated bilirubin and unconjugated bilirubin levels (8.25 mg/dL, 4.36 IU/L, 2.89 IU/L respectively), and thick blood film: *Plasmodium falciparum* ++++.

Based on clinical presentations, laboratory findings and parasitological examination, the patient was diagnosed as severe malaria with jaundice.

Jaundice in malaria may occur due to hemolysis, liver parenchymal disorder and cholestasis.⁶ Study

by Datau et al² in Minahasa, North Sulawesi demonstrated that most jaundice cases in malaria were mixed-type (78.6%). Liver function disorder (elevated SGOT and SGPT levels) and liver enlargement with pain on palpation are also found.⁶

A differential diagnosis of malaria with jaundice is bilious remittent fever, which is characterized by coffee-ground vomiting, diarrhea with bile and blood, painful liver enlargement, progressive jaundice, remittent fever, elevated bilirubin levels of over 10 mg/dL, moderately elevated SGOT and SGPT levels (rarely reach 500 IU/L), albumin, bilirubin, cylinder cast and hyaline cast in urine. Patients can fall into acute renal failure and die due to cardiovascular collapse.⁵ Based on clinical presentation and laboratory findings, this patient did not suffer from bilious remittent fever.

Joshi et al⁸ reported 9 patients with acute liver failure caused by *Plasmodium falciparum* infection in India. In those patients, they found encephalopathy due to liver impairment and toxemia, elevated bilirubin levels (especially the conjugated fraction), elevated SGOT and SGPT levels (mean value 91 IU/L and 70 IU/L respectively), elevated alkaline phosphatase levels, and prolonged prothrombin time. Liver biopsies demonstrated hyperplastic Kupffer cells containing malarial pigment, centrilobular hepatocellular necrosis with focal inflammation reaction and ballooning degeneration. Srivastava et al⁹ reported 7 cases of *falciparum* malaria with acute liver in India, where four of them died. Post-mortem liver biopsies demonstrated similar findings with those of Joshi et al's. We did not perform liver biopsy in this patient.

The management of severe malaria with jaundice is, in general, the same as of other severe malaria cases, which is by using parenteral quinine or artemisinin (qinghaosu) derivatives. Quinine is given by infusion with a dose of 10 mg/kg body weight in isotonic fluid for 4 hours, three times per 24 hours during at least 48 hours or until patients can take oral medicines.^{1,10,11} Quinine infusion is continued with sulfate quinine tablet 200 mg 3 x 2 until the seventh day.¹²

White et al,¹³ in studies in Thailand, recommended the use of a loading dose of 20 mg/kg body weight of quinine dihydrochloride in 4-hour infusion to rapidly and safely reach a therapeutic level (10 mg/L), followed by a dose of 10 mg/kg body weight every 8 hours. Pasvol et al¹⁴ found that a loading dose of quinine gave better response and more rapid parasite clearance. A report from Thailand by White et al⁶ in 1994 revealed quinine that had been used for more than 350 years as anti-malarial agent, began to show decreased therapeutic

response and increased resistance. However, Hall¹⁵ found that a loading dose was dangerous, since plasma quinine level >10 mg/L (30.8 mmol/L) often led to toxic effect. There even has been a report of a patient entering a coma with a plasma quinine level of 8.4 mg/L. Besides, quinine levels of over 10 mg/L increase the risk of permanent ocular damage. Greenberg et al¹⁶ used a dose of 10 mg/kg body weight every 8 hours for 3 days, followed by sulfate quinine tablet, for treating children with severe malaria in Zaire. They found a mean fever clearance time of 44.1 hours, and a mean parasite clearance time of 59.6 hours. This demonstrated that such dose gave effective results. Harijanto,¹⁷ in a study in Minahasa, North Sulawesi reported that a quinine dose of 10 mg/kg body weight/8 hours was as effective as a loading dose. At present, other anti-malarial drugs used to treat severe malaria are artemisinin derivatives (artemether intramuscular or artesunate intravenous). A meta-analysis from 7 studies in Thailand and Vietnam demonstrated that there were no significant differences between parenteral quinine and artemether in fever clearance time, recovery of consciousness, mortality rate (17% vs.14%).^{18,19} The same result was reported by Faiz et al²⁰ from Bangladesh. The adverse effects of artemisinin reported were abdominal pain, diarrhea, reduced reticulocyte count. Artesunate is more rapid-acting than quinine in terms of parasite clearance, is safer, and is simpler to administer. A randomized multicenter study by the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial) Group in Indonesia, India, Myanmar and Bangladesh, which involved 1,461 patients from June 2003 to May 2005, demonstrated a significant difference in mortality rate between the quinine group and the artesunate group (22% vs. 15%, $p = 0.0002$; absolute reduction of 34.7%).²¹

In plasmodium infection, the volume distribution of quinine decreases and systemic clearance also decreases in proportion to the severity of disease, causing higher plasma quinine levels in uncomplicated malaria patients compared to in healthy individuals, and the highest level occurs in patients with severe malaria. Elimination half-life is 18 hours in cerebral malaria, 16 hours in uncomplicated malaria and 11 hours in healthy people.⁶ In the human body, 80% of quinine undergoes biotransformation in the liver and 20% is excreted without any changes through the kidneys. Quinine is primarily bound to the acute phase plasma protein alpha-1 acid glycoprotein (AGP). Quinine binding by AGP will increase in severe malaria (>90%, while in healthy people 75–80%). The therapeutic effect and toxic effect of quinine are determined by free quinine level. In severe malaria, although total quinine level is high, the proportion of

free quinine is lower due to AGP binding (free quinine concentration is approximately 5–10%), and, therefore serious quinine toxic effects are rare.⁶

Dangerous quinine toxic effects, although not frequent, are hypotension, arrhythmia, shock, and central nervous system damage (blindness, deafness).²² If necessary, plasma quinine level can be measured using high performance liquid chromatography (HPLC) method with a sensitivity of 59% and a specificity of 79%. Another more sensitive, specific, simple and rapid (10 minutes) method is by using a dipstick for quinine-specific monoclonal antibody.²²

This patient was given 500 mg of quinine dihydrochloride in 500 ml of 5% dextrose per 8 hours for 36 hours, followed by 3 x 2 x 200 mg of sulfate quinine tablets until the seventh day. The patient also received an anti-emetic (metoclopramide), antacid syrup, and intravenous vitamin K, because the patient had severe liver impairment characterized by elevated total bilirubin, and conjugated bilirubin and transaminase levels that could impair vitamin K-dependent coagulation factors synthesis in the liver and because there was subconjunctival bleeding. Diarrhea was treated using fluid rehydration and atropine.

Premature ventricular contraction (PVC) may occur in healthy people or people with heart disease. The prevalence of PVC increases with older age, smoking, drinking coffee, anxiety, myocardial ischemia, electrolyte disorder (potassium imbalance), and pro-arrhythmic drugs (for example quinine, which may prolong repolarization time of heart muscle and in ECG is seen as prolonged QTc interval).²³ Quinine like quinidine is a chincona alkaloid that has anti-arrhythmic property, although it also pro-arrhythmia that can cause various arrhythmias such as block or extra-systole. In this case report, the patient had palpitations, and from ECG recording, we found multiple PVC. The drug of choice for treating multiple PVC with a frequency of over 5 times per minute is parenteral lidocaine. Lidocaine is given in a dose of 1–2 mg/kg body weight (50–100 mg) intravenously, followed by 1–4 mg/minute.^{23,24} Lidocaine is a class IB anti-arrhythmia agent that acts by blocking sodium channel, inhibiting slope action potential in phase 0, shortening effective refractory period and shortening action potential in Purkinje fibers, inhibiting spontaneous depolarization and reducing automation in the Purkinje system. Effective drug level is reached soon after intravenous administration. The adverse effects of lidocaine are delirium, convulsion, and bradycardia.²⁴

Hypokalemia decreases myocardial repolarization, therefore, prolonging recovery time. ECG findings in hypokalemia are not specific, including prolonged PR

interval, flat or inverted T wave, ST segment depression, prominent U wave, prolonged QT interval. ECG changes in hypokalemia can be found in 78% of patients with potassium level of <2.7 meq/L, 35% of patients with potassium level of 2.7 – 3.0 meq/L, and 10% of those with a potassium level 3.0 – 3.5 meq/L.²⁵ Premature ventricular contraction often occurs in hypokalemic states.

In this case, on the second day the patient felt tinnitus, hearing loss (this demonstrated adverse effects of quinine, which means that the patient was sensitive to parenteral quinine), palpitation, distended abdomen, and diarrhea. ECG demonstrated multiple PVC with a frequency of over 5 times per minute, trigemini, and sino-atrial block. The patient was diagnosed with severe malaria (jaundice) with arrhythmia. The presence of PVC and SA block supported the effect of quinine in a patient without any history of heart diseases, regular heart beat on admission, and then had arrhythmia after administration of quinine. We could not measure plasma quinine levels due to lack of facility. It was very probable that the plasma free-quinine level increased because patient had serious liver impairment indicated by elevated SGOT, SGPT, total bilirubin and conjugated bilirubin levels, whereas 80% of quinine is metabolized in liver. This patient also had mild hypokalemia, which was probably caused by diarrhea and vomiting. In a hypokalemic state, quinine induced- arrhythmia could happen easily. These two factors, parenteral quinine and hypokalemia, increased the risk of arrhythmia in this patient, although the role of hypokalemia was little (it was only mild hypokalemia, and was not supported by ECG recording).

The management of this patient was with 50 mg intravenous bolus of lidocaine, followed by 1500 mg infusion in 500 ml 5% dextrose for 24 hours to suppress arrhythmia, while quinine infusion was terminated and was changed to sulfate quinine tablets. Observation on following days demonstrated improvement in the patient's condition (there was no arrhythmia).

The prognosis of this patient was good because he demonstrated a good response to quinine (no fever on the third day, malarial blood smear Plasmodium falciparum ++++ on admission became ++ on the second day, and on the third day). In addition, the liver function test demonstrated improvement, bilirubin reached almost normal levels, and there was no arrhythmia after treatment with lidocaine.

CONCLUSION

We have discussed a case of severe malaria with jaundice in a 25 year old male patient who also had arrhythmias (multiple PVC and SA block) while receiving quinine infusion. The treatment of arrhythmias was with intravenous bolus of lidocaine followed by continuous infusion for 24 hours, and replacement of quinine infusion with sulfate quinine tablets. The patient also got potassium supplementation because he had mild hypokalemia due to vomiting and diarrhea. Administration of parenteral quinine must be performed carefully because of its pro-arrhythmic effect, especially in older patients who have heart diseases or patients with electrolyte disorder (hypokalemia) which frequently occurs in malaria, due to vomiting and or diarrhea.

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