بسم الله الرحمن الرحيم

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Low Dose Quinine For Treatment Of Chloroquine Resistant Falciparum Malaria.

By

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Dedication

I dedicate this thesis to my brother ***Nour Eldin.***

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In preparation of this thesis I have received assistance from many sources, and I am deeply grateful to all those who supported me

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Abstract

The current recommended dose of 10mg quinine/kg body weight 3 times a day for 7 days for treatment of chloroquine resistant falciparum malaria is so high that many patients may suffer cinchonism. In order to identify the lowest effective dose of quinine for treatment of chloroquine resistant malaria, we enrolled ninety three patients who presented to the health centre at Elhara Eloula, New halfa, Eastern Sudan with symptoms of malaria after completing the full dose of chloroquine. The patients were randomized in three treatment groups for quinine treatment. They received quinine for 7 days as follow: 10mg/kg thrice daily (group I, 32 patients), 10mg/kg twice daily (group 2,31 patients) and 15mg/kg once daily (group 3,30 patients). All patients were followed daily for 7 days and then weekly for 3 weeks. There was no significant differnce in parasite clearance time between the three groups. Parasitaemia was detected during the follow- up on day 28 or earlier in 2/32(6.3%), 5/31(16.1%) and 5/30(16.7%) in the three groups, respectively; this differnce was not significant. In 75% of these patients the parasitaemia was due to true recrudescence, as confirmed by parasite genotyping . Thus, the data in this study showed that low dose of quinine can be prescribed to treat chloroquine resistant falciparum malaria in Sudan with comparable outcome to high quinine dose.

بسم الله الرحمن الرحيم

الخلاصة

إن جرعة الكينين الموصى بها حالياً والبالغة 10ملغم/كجم من وزن الجسم ثلاثة مرات يومياً لمدة أسبوع لمعالجة ملاريا الفالسيبارم المقاومة للكلوروكوين، هي جرعة كبيرة لدرجة أن كثير من المرضى قد يعانون من أعراض التسمم بالكينين.

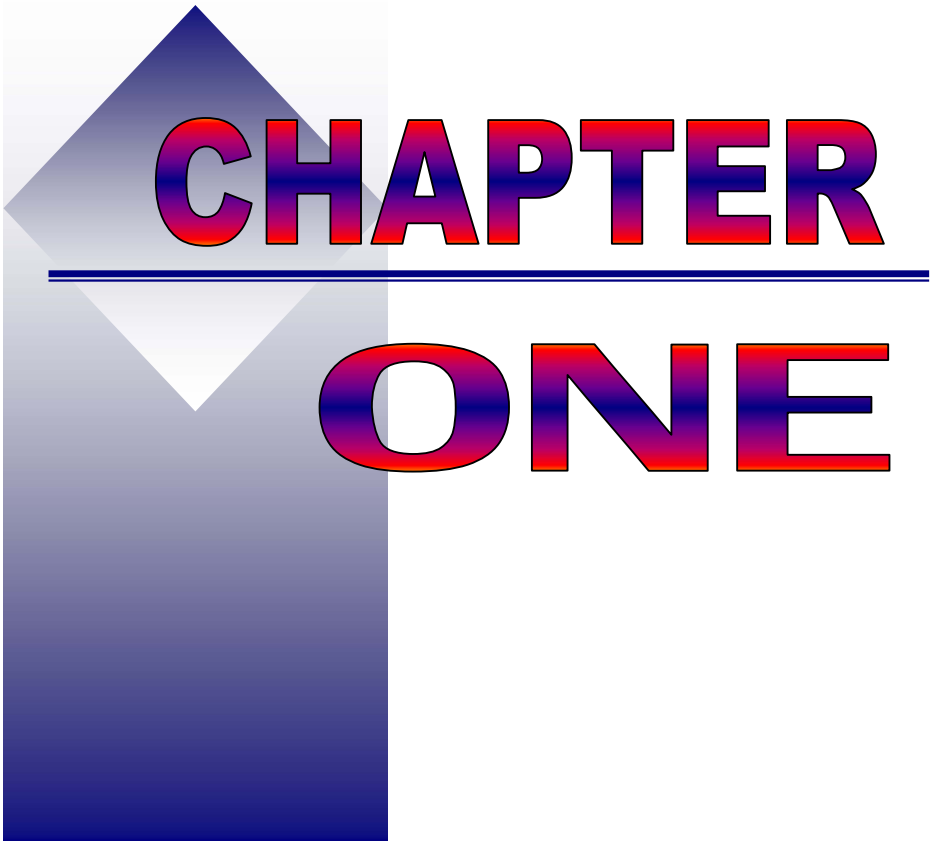
من أجل التعرف علي أقل جرعة من الكينين لمعالجة الملاريا المقاومة للكلوروكين, فقد قمنا بتقسيم ثلاثة وتسعون مريضا من الذين حضروا للمركز الصحى بالحارة الأولي بحلفا الجديدة ,شرق السودان بعد أن أكملوا المدة المقررة للعلاج بالكلوروكوين ألى ثلاثة مجموعات عشوائيا لمعالجتهم بالكينين.

جميع المرضى عولجوا بالكينين لمدة أسبوع كما يلى:- المجموعة الأولى (32مريضا) تلقت الكينين 10ملجم/كجم من وزن الجسم ثلاثة مرات يوميا, المجموعة الثانية (31 مريضا) تلقت 10ملجم/كجم مرتين يوميا والمجموعة الثالثة (30 مريضا) تلقت 15ملجم/كجم مرة واحدة يوميا.

كل المرضى تمت متابعتهم يوميا لمدة أسبوع ثم أسبوعيا لمدة ثلاثة أسابيع. ليس هناك فرق فى زمن التخلص من طفيلى الملاريا من الدم بين المجموعات الثلاثة. اثناء المتابعة وجدت الطفيليات فى الدم فى اليوم الثامن والعشرين أو قبلة فى 2(6.3%) من المجموعة الأولى, 5(16.5%) من المجموعة الثانية و5(16.7%) من المجموعة الثالثة. بعد الفحص الجينى للطفيلى, فقد اتضح أنة فى 75% من تلك الحالات يعزى ظهور الطفيليات لتنشيط الأصابة مرة أخرى.

من هذه الدراسة يتضح أن الجرعة المخفضة من الكينين يمكن استعمالها لعلاج الملاريا المقاومة للكلوروكوين فى السودان مع اعطاء نتائج مشابهة للجرعات الكبيرة.

Contents


CHAPTER
ONE

Introduction & Literature Review

Malaria:

In Sudan malaria is a major health problem accounting for about 40% of all infectious disease and ***plasmodium falciparum*** is the predominant species, which is responsible for over 90% of the infection[1].

One of the essential elements in control of the disease is appropriate management and chemotherapy to reduce morbidity and to prevent mortality. Unfortunately, falciparum malaria is becoming increasingly resistant, in most of the endemic areas world wide, to most available drugs including chloroquine and quinine[2].

This grave concern was deepened by reality that there is no available effective vaccines until now.

In order to increase compliance , it would be an advantage to reduce the total daily dose and the number of daily doses to minimum. We therefore decided to evaluate once daily dose of quinine giving 15mg/kg/ daily with thrice daily doses giving 10mg/kg/ dose and twice daily doses giving 10mg/kg/dose for treatment of chloroquine resistant malaria.

Malaria and Chloroquine Resistance in Sudan

Chloroquine has been in use for treatment of malaria in Sudan for more than 40 years. The possible occurrence of chloroquine resistant forms of falciparum malaria in Sudan was initially suggested in 1978 in the Central Sudan where 0.4% and o.2% of the patients were having R1 and R11 resistance, respectively [3]. Few years later, in Wad Medani (Central Sudan), all grades of chloroquine resistance were reported in children, where 25% of the parasite isolates from patients were chloroquine resistant; 8.3% were late R1 and 16.7% were RIII[4].

In the capital Khartoum resistanc to chloroquine was found to be 61.5%; 34.6% as R1 and 26.9% as RII [5]. Recently, High level of chloroquine resistance (75%) was seen among 280 falciparum patients visiting Omdurman Hospital[6]. This rapid increase in resistance may be partially due to social and environmental changes occurring in the area [7].

In Eastern Sudan the situation of the chloroquine resistance is also serious. It was reported that 42% of the patients treated with chloroquine were resistant, 16% with severe RIII forms of resistance [8]. In New Halfa (Eastern Sudan), among 26 patients treated with chloroquine, 76.9% were found to be resistant; 53.8% were early RI, 7.7% were late RI and 15.4% were R III [9].

From the above data it is clear that chloroquine resistance is spreading widely and rapidly in Sudan reaching alarming high percentage.

History

The malaria parasites that infect human are species of the genus plasmodium of the class sporozoa in which the asexual cycle (Schizogony) takes place in the red blood cells of the vertebrate and the sexual cycle (Sporogony) in the mosquitoes. The members of this genus which causes malaria in mammals, have close similarities in morphology and life cycles .

Malaria, paludism, intermittent fever, chills, Roman fever, charges fever, march fever, tropical fever and coastal fever are different names given to malaria .

The term malaria is derived from two different Italian words , mal (Bad) and aria (Air) . Hippocrate divided miasmic fever into continuous, quartan and tertian fever .

In 1638, the countess El Cinchona , wife of the vice roy of Peru, was cured from malaria by bark of certain trees, later called cinchona , from which quinine was later extracted .

Malaria species:

P. Malariae was described in 1880 by Laveran , P.Vivax was named. In 1890 by Grassi and Feletti , ***P. Falciparum*** in 1897 by Wechi and ***P. Ovale*** in 1922 by Stephen . In 1898 Ros published a description of sporogony of the avian species ***P.Relictum*** in culucine mosquitoes.

Yet it was not until 1948 that Short et al. demonstrated the exoerythrocytic cycle of human malaria parasites [10] .

Life cycle :-

The life cycle of the plasmodia takes place in two hosts, vertebrate and mosquitoes. The asexual cycle in the vertebrate host is known as schizogony , and the sexual cycle in the mosquito as sporogony.

Schizogony :-

The infectious sporozoites from salivary glands of an infected female anophline mosquito are injected during biting into human blood stream within 30 minutes. The slender, motile organism enters the liver parenchymal cells initiating the exoerythrocytic cycle. Within the liver cells the parasite begins an extensive multiplication and are called schizonts, which produce thousands of merozoites 8 – 15 days later depending upon the species of the plasmodia . The parasitized liver cells eventually ruptured freeing the merozoites in the blood stream to initiate the erythrocytic cycle. Some schizonts of ***P. vivax*** and ***P. Ovale*** may remain in the liver cells (Hypnozoites) which are responsible for later relapses, however, in ***P. Falciparum***, in which true relapses do not occur, the hepatic schizonts apparently survive only for short time. A relapse signifies that parasitaemia develops from exoerythrocytic stage in the liver. A recrudescence means an increase in parasites count that has persisted at low level in the blood.

The erythrocytic cycle consists of invasion of red cells by merozoites, their development through trophozoites, then schizonts, the rupturing of the cells and re- invasion of new cells. As repeated

cycles of asexual multiplication occur, some parasites which invade red cells do not undergo division as schizonts, but instead are transformed into male and female gametocytes.

Sporogony :-

Sporogony, the sexual cycle, takes place in the mosquito. The gametocyte are ingested with the blood meal, unlike schizonts, they are not digested. The male is known as microgametocyte while the female as macrogametocyte. After maturation, fertilization will occur forming the zygote. Within 12 – 24 hours after the mosquito's meal, the zygote changes into a wormlike form called the ookinete, which penetrate the wall of the mosquito gut and develops into spherical oocyte between the epithelium and the basement membrane. Here it increases to many times its original size, with thousands of sporozoites developing inside . After the rupture of oocyte, sporozoites will enter the body cavity and migrate to salivary glands. When the mosquito feeds on human, the sporozoites gain access to the blood and tissues to begin exoerythrocytic cycle . The sporogony takes 10–17 days .Transmission of malaria may occur by other mechanisms such as blood transfusion, contaminated syringes or across the placenta [10].

Epidemiology of malaria

Malaria remains the most important of the tropical diseases. The spread is wide through the tropics, but also occurring in many temperate regions. Each year there are 300 – 500 millions clinical cases of malaria. About 40% of the world population is at risk of acquiring the disease. (11)

P. Flciparum predominate in sub-sahran Africa, New Guinea and Haiti .While ***P.Vivax*** is more common in Central America and the Indian sub-continent, an increase in ***P. Flciparum*** has occurred in Indian sub-continent over the past decade. The prevalence of these two species is approximately equal in South America and Eastern Asia. ***P. Malaria*** is found in most areas (Particulary in west and central Africa) but is less common. ***P. Ovale*** is relatively unusual outside Africa.(12)

The manifestation of malaria in people who grow up in endemic areas vary with the degree of endemicity, the age of the patient and the development of immunity.

In hypoendemic area little immunity is acquired, epidemics of malaria are liable to occur, less than 10% of children have parasitaemia and palpable spleen.

In mesoendemic areas malaria is frequent, but only seasonal , 11-50% of children have parasitaemia and palpable spleen. Repeated infections lead to anaemia and ill health.

In hyperendemic areas malaria transmission takes place all over the year, but with seasonal increases, 51 - 75% of children have

parasitaemia and palpable spleen, adult develop occasional short bouts of fever.

In holoendemic areas malaria is intense throughout the year, more than 75% of children develop palpable spleen and parasitaemia.

Three characteristics mainly determine the difference in epidemiology of malaria are seen. They are :- the density, biting habit and longevity of the mosquitoes.

Density is the number of vectors present in place relative to human population, as might be expected, malaria transmission will tend to be proportional to mosquitoes density. A mosquito that frequently bite will have a greater chance of both picking up and passing on the parasite; this factor has a large effect on malaria transmission. Once the mosquito became infected, it will remain so for her rest of life; this longevity has greater influence on malaria transmission.

In Sudan malaria is one of the most serious health problems, accounting for some 40 % of all infectious diseases. The predominant parasite is ***p. falciparum***, which is responsible for 90 % of all reported malaria cases [1].

Traditionally the southern part of the country was considered to be holoendemic with malaria. The disease has spread across the country to many regions, previously known to be free of the disease. The fast spread of the disease has made central Sudan, Khartoum province and even the northern part holoendemic with malaria [7]. The reasons for the spread are:-

1. Heavy rains and flood all over the country occurring in 1988, 1992, 1994 and the successive years.
2. Deterioration of the environmental health.
3. Mass migration of the refugees, many of whom are human carriers of malaria from the south to all parts of the country[13].

Resistance of the parasite to choloroquine is now well documented, this was initially suggested in 1978 in Jazira [3]. However, later studies conducted at central Sudan [5] and eastern Sudan [8], confirmed the presence of the resistance.

Pathophysiology

The spectrum of the pathological process differs with changes in the degree of endemicity. In the areas of high endemicity, the greatest to suffer are children less than five years of age, whereas in areas of low endemicty, the disease affects all age groups.

The pathological changes associated with all types of malaria have certain features in common, but the best known are those for ***P. Falciparum*** malaria. A peculiar feature of ***P.Falciparum*** is ability of the parasitized cells to adhere to venular endothelium (cytoadherence). These parasitized cells remained attached until the merozoites are formed and released to invade other erythrocytes. Thus the predominant forms seen in the peripheral circulation are the erythrocytes infected with the ring stage. Soluble products of plasmodia species known as malarial toxins cause systemic release of proinflammatory cytokines such as tumour necrosis factor (T.N.F) which acts on many other systems like endothelium.

The parasite antigens may stimulate T-cells to secrete, or induce production of cytokines from other cells. Some T-cells subset secrete interferons and other cytokines and may facilitate production of T.N.F by monocytes; this may have potentiality to be involved in the disease pathogenesis. Both interferons and T.N.F may play roles in dyserythropoeitic anaemia, and T.N.F may contribute to cerebral malaria as a result of up-regulation of intracellular adhesion

molecule-1 (ICAM-1) in cerebral blood vessels endothelium which acts as a cytoadherence receptor for ***P.Falciparum***, and probably it is the major vascular ligand for cytoadherence within the brain[14]. The apparent adverse effect of pro-inflammatory cytokines on the host are balanced by evidence of their antiparasitic effect. These cytokines synergize with others defense mechanisms to limit parasite multiplication. On the other hand, interleukin-10 (IL-10) inhibit the ability of malarial antigens to induce or release T.N.F, and severe malaria is associated with low level of IL-10 [14].

Anaemia:

Anaemia is an inevitable consequence of malaria, especially in children[15]. Its development is directly related to density of parasitaemia. The mechanisms are multifactorial and complex, involving haemolysis and inappropriate bone marrow response [16]. Cytokines, notably T.N.F, are known to depress erythropoiesis and contribute to dyserythropoiesis. Immune mediated haemolysis has been suggested as the mechanism of anaemia among children in the holoendemic area of West Africa. There was evidence that red cells were synsitized with C3[17].

Jaundice:

Hyperbilirubinaemia is attributable to intravascular haemolysis of parasitized erythrocytes, hepatic dysfunction, and possibly an element of microangiopathic haemolysis associated with disseminated

intravascular coagulation (DIC) and it is more common in adult than in children [18].

Liver dysfunction may affect drugs clearance and contributes to lactic acidosis. There is sequestration in hepatic microvasculature, and in severe infection liver blood flow compromised. Acute malaria adversely affects the function of broad array of cytochrome P450 microsomal enzymes and also impair conjugation reactions. Liver biopsy usually reveals Kupffer cells hyperplasia and mononuclear cells infiltration[18].

Cerebral Malaria

Any pathophysiological explanation of the mechanism underlying cerebral malaria must take into account the clinical and the pathological features of this condition. The mortality of cerebral malaria ranges from 10 to 50% in treated patients [19].Unfortunately there is no animal model which satisfactory reproduce either the clinical or the pathological features of cerebral malaria in human [20]. This has hampered progress in understanding the pathophysiological mechanisms, and has led to several hypothesis to explain the pathophysiology:

A-Mechanical hypothesis

This hypothesis attempts to explain the pathophysiology of severe falciparum malaria by microcirculatory obstruction, with resultant local hypoxia and substrate depletion. Two principal mechanisms have been proposed to account for such

obstruction, but in both cases there is congestion of capillaries with red cells containing mature trophozoites and schizonts.

1-Decreased deformability:-

Normal erythrocytes must undergo considerable deformation in order to transfer through the capillaries, and when erythrocytes are unusually rigid, obstruction may occur. This best illustrated in the crises of sickle cell disease. It has been argued that erythrocytes containing mature parasites might be retained in the capillaries by similar mechanism. Studies have shown that ***P.Falciparum*** infected erythrocytes have reduced deformability, which is directly proportional to the maturity of the intracellular parasite [21].

1- Cytoadherence:-

Pathological studies suggest intimate opposition of endothelial and infected erythrocytes membranes and this has led to a belief that there is a specific molecular interaction which causes infected erythrocyte to adhere physically to endothelium. Uninfected erythrocytes will also bind to the surfaces of erythrocytes containing mature forms of the parasite by a mechanism similar to that of cytoadherence to endothelial cells causing rosetting. This may be important in the sequence of events leading to microvasculature obstruction, but has not been demonstrated in vivo in human [22].

B- The immunological hypothesis

The immune mechanism appear to be important in the pathogenesis of cerebral malaria in mice [23]. Malaria infections induce both cellular and humoral immune responses, and there is evidence of complement activation in acute malaria in man [24].Immunity is stage specific, in that immunity to either sporozoites challenge or to gametocytes transmission does not protect against asexual form, also it is specific for parasite species, strain, and antigenic variant within a strain [25]. The neuropathological findings in cerebral malaria have been interpreted as resulting from hyperergic reaction of the central nervous system to the antigenic challenge of ***P. Falciparum*** infection [26].

Gastrointestinal dysfunction

Minor ulcerations of the stomach and duodenum is common in severe malaria. The pattern of malsabsorption of sugar, fat and aminoacid, suggests splanchnic hypoperfusion [27,28,29,30]. This results from gut sequestration and visceral vasoconstriction, and there may be increased gut permeability or reduced local defense against bacterial infection. Antimalarial drugs absorption is remarkably unaffected in uncomplicated malaria [31].

Spleen

There is considerable splenic enlargement in malaria, an increase in capacity of the spleen to clear red cells from the circulation both by receptor mediated (immune) mechanism [32,33] and by

recognition of reduced deformability[34]. The spleen may also modulate cytoadherence and plays a role in limiting the acute expansion of malaria infection by removing parasitized erythrocytes and this has led to suggestion that failure to augment splenic clearance sufficiently and rapidly may be a factor in development of severe malaria [35,36].

Metabolic dysfunction

In severe malaria, arterial, venous, capillary and cerebrospinal fluid concentration of lactate rises in direct proportion to severity of the disease. Lactic acidosis is an important cause of death and it results from several discrete processes:- the tissue anaerobic glycolysis consequent upon microvasculature obustruction, failure of hepatic and renal lactate clearance and production of lactate by the parasite [37,38,39]. Mature malaria parasite consume up to 70 times as much glucose as an uninfected cell, and over **90%** of it converted to lactic acid. Plasmodia do not have complete set of enzymes necessary for citric acid cycles. Lactate level also rise after generalized convulsions. Hyperlactataemia is accompanied by hyperalaninaemia, reflecting the impairment of gluconeogenesis [40] ; lactate and alanine are the major precursors for gluconeogenesis. Triglyceride and free fatty acids levels are also elevated in acute malaria[41].

In severe malaria there is dysfunction of all organ systems, particularly those with obligatory high metabolic rates. Pitutary-

thyroid axis abnormalities result in sick thyroid syndrome and also parathyroid dysfunction [42], by contrast the pitutary-adrenal axis appears normal in acute malaria [43].

Hypoglycaemia

Hypoglycaemia is increasingly recognized as a complication of falciparum malaria and it's treatment. Usually it is not suspected clinically because of the patient poor clinical state. Hypoglycaemia complicates malaria in three clinical settings which may overlap:-in patients given quinine, in pregnant women and in patients with severe disease. Quinine induced hyperinsulinaemia was the commenest cause of hypoglycaemia in Thailand; it was seen in adult, pregnant women and in children [40], and has also been reported in adult and in children in Zair [44] and in adult in India[45]. Pregnant women may develop hypoglycaemia with or without quinine treatment [46]. Hypoglycaemia has been found in adult with severe manifestations such as cerebral malaria, severe anaemia, jaundice, high parasitaemia and lactic acidosis at a time when their plasma insulin level was relatively low before quinine therapy [40].

Hypoglycaemia is associated with hyperlactaemia and share the same pathophysiological etiology. The factors participate for hypoglycaemia include:- an increase in peripheral requirement for glucose consequent upon anaerobic glycolysis and increased metabolic demand of febrile illness, the obligatory demands of the

parasites which use glucose as their major fuel and failure of hepatic gluconeogenesis [37,40].

Renal failure

P.Falciparum malaria was the second cause of renal failure in Ethiopia [47]. Many patients are dehydrated and the kidney function usually return to normal after dehydration. This hypoperfusion may result in cortical vasoconstriction, ischaemia and later tubular necrosis [48]. Renal microvascular obstruction may occur due to sequestration in the kidney or may be due to immunological factors [49].

Black water fever

This syndrome caused by severe haemolysis with resultant haemoglubinuria, it is rarely seen now, and may occur in patients with overwhelming infection or with red cell abnormalities like G6PD deficiency who use quinine or primaquine for malarial treatment. This syndrome associated with high mortality(20-30%)documented in European and Asian working in Africa in the first half of twentieth century [50]. Half of these deaths were caused by renal failure in patients partially treated with quinine.

Pulmonary edema

This is a grave and usually fatal manifestation of severe falciparum malaria . A proportion of cases show evidence of fluid overload, with raised central venous or pulmonary arterial wedge pressures [51], others develop pulmonary edema with normal or negative fluid balance and in the face of normal or reduced

pulmonary wedge pressures [52]. Unlike the capillary permeability in other vascular beds, the capillary permeability in pulmonary beds showed a sudden increase and this may be the explanation of pulmonary edema [53].

Clinical Features

Plasmodium Vivax and *Plasmodium Ovale* Malaria

In many cases the illness starts with a period of several days of continuous fever before the classical periodic fever with rigors occur. The patient feels cold and the temperature rises to about 40c^{o}, after short time the hot or flushing phase begins, it lasts several hours and gives way to a profuse perspiration and gradual fall in temperature. The cycle is repeated 48 hours later. Gradually the spleen and liver enlarge and may become tender, anemia develops slowly, ***H.Simplex*** is common. Relapses are common in the first two years.

Plasmodium Malariae Infection

This usually associated with mild symptoms and bouts of fever every third day. Parasitaemia may persist for several years with occasional recrudescences. It is a recognized cause of nephritic syndrome.

Plasmodium Falciparum Infection

This is more dangerous than the other forms of malaria. The onset, especially of primary attack, is often insidious with malaise, headache, vomiting, cough and mild diarrhoea. The fever has no particular pattern and does not usually rise quite so high as in other forms of malaria. Hot, cold and sweating stages are seldom seen. The liver and spleen enlarge and became tender. Anaemia develop rapidly. Jaundice is common due to haemolysis and hepatitis [(10)].

Parasitological Diagnosis

Parasitological examination of the blood should be available in the primary health care units and should incorporated into patient management as soon as possible. The presence of malaria parasite in the blood may be detected by routine thick blood film examination when densities are in the order of 5-10 parasite /ml.of blood. Thick blood films are more useful than thin films in the detection of low parasitaemia. Malaria parasites may, occasionally, be discovered in the examination of poorly prepared slide or in thin blood films prepared for differential blood count. Thick blood films yield a much higher concentration of parasite than thin films, it is useful when the parasites are few or thin films are negative. The thick film is not a thick drop, but the smear spreads at thickness of 0,5 mm or less, so that it is sufficiently transparent for microscopic examination when haemoglobin is removed.

Thick blood films are not fixed with alcohol, but the slide with the dried thick film is placed in 50 ml diluted Geimsa stain. After 45 minutes of staining, the smear is carefully rinsed with tap or buffered water and then allowed to dry; 5 minutes search of a thick film should reveal parasites if present. The stained thin dry film permits the study of the morphology of the parasite more better than thick film. Recent studies on the parasite genome together with the production of pure malarial antigens and specific monoclonal antibodies, have resulted in development of immuno - chromatography test (ICT). This test is especially useful when the

patient has repeated negative films, or the patient received antimalarial treatment for several days and the blood film was negative.

Chemotherapy of Malaria

Chloroquine

It is 4-aminoquinolone compound, rapidly absorbed after oral administration. In adult with malaria, oral bioavailability related to parenteral treatment is 70%. Intramuscular and subcutaneous administrations of chloroquine give almost identical plasma or whole blood concentration profile. Peak plasma concentration reached in about 30 minutes after parenteral administration, this will result in high and potentially toxic blood concentration if doses of 5 mg base/kg or larger are given. Chloroquine has enormous volume of distribution, which results from considerable binding in organs such as liver, connective tissues and melanin containing tissues such as skin and retina. Chloroquine is 55% protein bound in plasma, concentration in cerebrospinal fluid (CSF) is very low with mean value of 2.7% of corresponding whole blood concentration [54]. The drug is 51% cleared unchanged by the kidney, is biotransformed by the liver, mainly to desethyl and bisesethyl chloroquine.The principal metabolite desethyl chloroquine is less potent than the parent compound and it is also eliminated more slowly. Although this metabolite contribute toward prophylactic efficiency, it's concentration is not relevant to the treatment of severe malaria. The terminal half life of chloroquine is approximately I-2 months, but for curative treatment, the biological half life is about 6- 10 days.

Acute Toxicity

Oral chloroquine is usually well tolerated, nausea, headache, uneasiness and dysphoria are relatively common; patients may vomit and may complain of blurred vision. Postural hypotension associated with malaria may be exacerbated by chloroquine and pruritis may be severe. Chloroquine over dose is manifested by hypotension, dysrhythmia, convulsion and coma.

Chronic Toxicity

Administration of chloroquine for long time - years – as a prophylactic or in case of rheumatoid arthritis was associated with significant risk of retinopathy. Skeletal and cardiac myopathy may also occur in patient receiving high dose of chloroquine. Chloroquine can aggravate psoriasis [55].

Quinine

Quinine is the treatment of choice for severe malaria. It is a cinchona alkaloid, quinine sulphate is well absorbed when given orally. Peak plasma concentration is reached in 1-3 hours. The parenteral form is quinine dihydrochloride which should not be given subcutanously because it can result in skin necrosis. When given intravenously, it should be diluted with normal saline or dextrose and given over 2-3 hours. Intramuscular quinine is certainly painful if concentrated acidic solution are administered. Quinine is a base and the principal plasma protein to which it binds is the acute

phase protein, which increases in malaria, and therefore during the illness quinine is less toxic.

Quinine is predominantly –80%- eliminated by hepatic biotransformation, first to 3 and 2- hydroxyquinine, and then to a series of more water soluble metabolites. 20% of the quinine is eliminated by the kidneys. The mean terminal elimination half life in healthy adult is 11 hours compared with 16 hours in uncomplicated malaria patient [51,52,53,54,55,56].

Toxicity

Minor adverse reactions are common with quinine therapy. A chracteristic symptoms complex known as cinchonism with a plasma concentration over 5mg/litre. This consists of tinnitus, high tone deafness, nausea, uneasiness, dysphoria, blurring of vission and vomiting. Severe toxicity may lead to hypotension, myocardial conduction disturbances, deafness, hypoglycaemia and coma. Quinine is a potent stimulant to pancreatic insulin secretion. Postural hypotension is common in acute malaria and this may be exacerbated by quinine therapy. Thrombocytopenia, Comb's positive haemolytic anaemia and other haemolytic reactions are rare [55].

Mefloquine

It is a quinolone methanol compound which structurally resemble quinine. It is effective against all malaria species including multi drug resistant ***P.Falciparum***, although resistant parasites population occur naturally. Mefloquine is well absorbed and highly

bound to plasma protein (98%), and exhibit a multiexponential decline in blood concentration with a terminal elimination half life of three weeks. Clearance is by hepatic biotransformation. No parenteral preparation is available, oral suspension is better absorbed than tablet[57].

Toxicity

Dizziness, nausea, vomiting and GIT upset are common. Headache, bradycardia, skin reactions and neuropsychiatric disturbances are rare manifestations [57].

Sulphadoxine-Pyrimethamine (Fansidar)

This is the most used of a family of drugs combination which antagonize parasite folic acid synthesis. They act by inhibition of dihydropteroate synthesis (sulphonamide) and dihydrofolate reductase synthesis (Pyrimethamine). The combination is well absorbed, plasma protein binding of both component in healthy subject is high (pyrimethamine 93%, sulphadoxine 88%). Pyrimethamine is cleared predominantly by hepatic biotransformation and the terminal elimination half life is approximately 90 hours. Only 5% of sulphadoxine is acetylated and secreted in the urine in this form, the terminal elimination half life is approximately 180 hours.

Toxicity

Oral sulphadoxine- pyrimethamine may provoke folate deficiency in vulnerable subjects (pregnant and malnourished

patients). Sulphonamide should not be given in late pregnancy or to the newborn because of the rare risk of provoking kernicterus. Severe allergic cutaneous reactions are the most common serious adverse reactions (erythema multiforme and Steven-Jonson syndrome). Agranulocytosis and other blood dyscrasias, hepatitis, pulmonary eosinophilia and neuropathy have been reported [58].

Qinghasosu (Artemisinin).

It is a sesquiterpene lactone peroxide extracted from leaves of the plant artemisia annua. Two derivatives are widely used: the lipid soluble methyl ether artemether, and the water soluble hemisuccinate derivative artesunate. These drugs are the most rapidly acting of the known antimalarials; they also have abroad time window of antimalarial effect from ring forms to mature trophozoites. Artemisinin is available as capsules of powder or as suppositories. Artemether is formulated in Sesame oil for intramuscular injection. Artesunate is formulated either as tablets or as dry powder of artesunic acid for injection, supplied with ampoule of 5% sodium bicarbonate. The powder is dissolved in sodium bicarbonate to form sodium artesunate, and then diluted in 5% dextrose or normal saline for intravenous or intramuscular injection. Artether is very similar compound to artemether. It is the oil soluble ethyl ether and will be given by intra muscular injection. Toxicity of the artemisinin related compounds such as depression of

reticulocyte count, neurotoxicity and gut toxicity appear rarely and at higher doses [57].

Halofantrine

This is a phenanthrene-methanol compound. It is dispensed in tablets and no parenteral preparation. The drug has low oral bioavailability; it is recommended that halofantrine doses are better divided in three doses at six hour intervals. Oral bioavailability can be increased two to three folds if the drug is taken with fatty meals. Halofantrine is almost entirely eliminated by hepatic biotransformation. The terminal elimination half life is 3-4 days.

Toxicity

Halofantrine is generally well tolerated. Abdominal pain and diarrhoea occur rarely. Intravascular haemolysis, cardiac toxicity and hypersensitivity reactions have been reported [58].

Primaquine

It is an 8- aminoquinolone compound. Absorption is essentially complete, peak plasma concentrations are reached in 6 hours. Effective clearance of tissue schizonts does not begin until primaquine udergone biodegradation by demethylation and oxidation to quinolone- quinone derivatives, the active antimalarial and haemolytic agents. Only 1% is excreted unchanged in the urine. It acts on the exorythrocytic stages and has practically no effect on

the erythrocytic stages. It postulated that both tissue schizonts and the G6PD deficient erythrocytes have a deficiency of an enzyme or cofactor in the pentose phosphate pathway, making them susceptible to oxidative dammage. Primaquine also has gametocidal effect, making it the best available drug to interrupt the transmission of malaria.

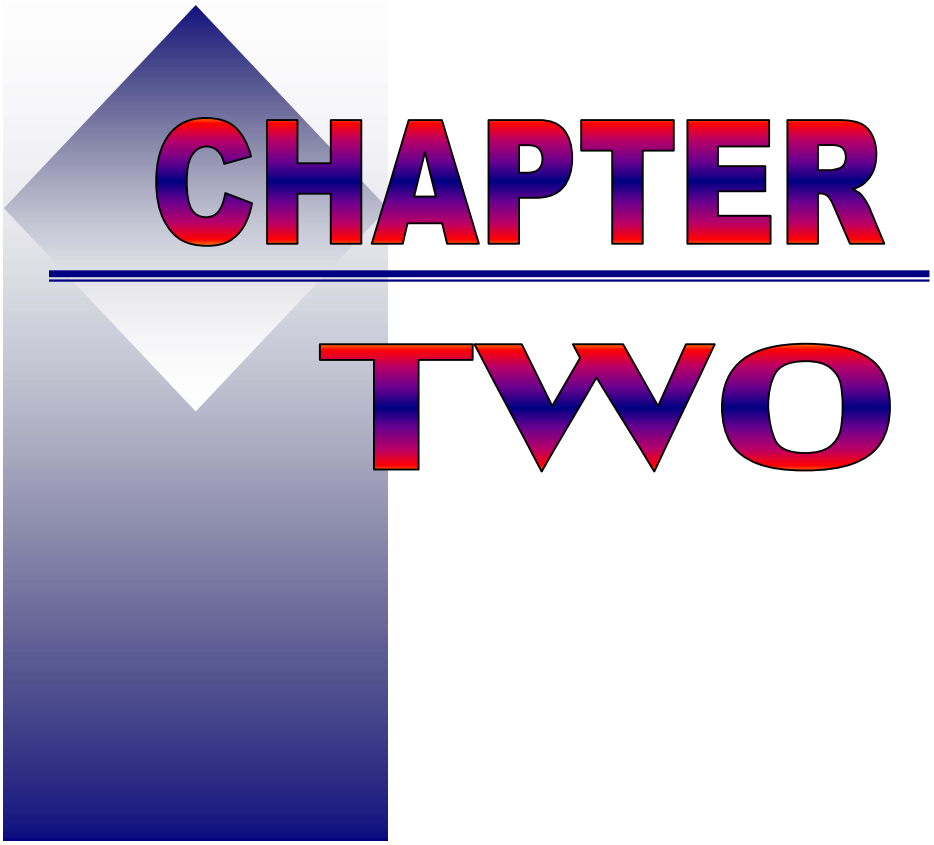
Toxicity

Toxic reactions often seen when large doses (60-240 mg) are given, including headache, pruritis, leucopenia and methaemoglbinaemia. Severe haemolysis occurs in susceptible individuals (58).

Objective

a. To evaluate the clinical and parasitological responses to different quinine doses.

b. To evaluate the toxicity and adverse drug reactions among the patients.


CHAPTER
TWO

Methodology

Study Area

The study was carried out in New Halfa, an agricultural area in Eastern Sudan, 500Km from khartoum. It is 450M above sea level, located between 15- 19 lat .North and 35- 36 long. East. The average annual rain fall is 238mm and the average relative humidity is 35%. There are two major agricultural schemes with permanent irrigation system. The area is made up of an isovillages constituting 400,000 individuals. The health services obtained by one teaching hospital, one single doctor hospital and 50 primary health centres. It is mesoendemic for malaria with a peak of transmission following the rainy season. The predominant malaria parasite is *P.Falciparum*.

Patients

Patients presented to the primary health centre (Elhara Eloula), during the study period, (Dec.2002 to Feb.2003) with symptoms suggestive of malaria after completing full course of chloroquine were included after verbal consent from the patients or the parents in case of children.

Exclusion Criteria

1-Pregnant women.

2-Chronic debilitating illness.

3-Patients with severe malaria. The diagnosis of severe malaria according to W.H.O criteria [59] was made if the patient presents with one or more of the following features:

1 –Cerebral malaria (unrousable coma), failure to localize or to make an appropriate verbal response to noxious stimulus.

2-Shock (circulatory collapse) systolic blood pressure of 80mm/Hg or less with cold extremities.

3-Jaundice detected clinically or when the total bilirubin is 3mg/dl or more.

4-Impairment of consciousness less marked than unrousable comma.

5-Prostration or weakness so that the patient can not sit or walk in the absence of obvious neurological explanation.

6-Severe anaemia, haemoglobin of less than 5gm/dl.

7-Pulmonary oedema.

8-Macroscopic haemoglobinuria.

9-Renal failure with serum creatinine more than 3mg/dl.

10-Repeated generalized convulsions – more than two observed within 24hours despite cooling.

11-Hypoglycaemia defined as blood glucose 40mg/dl or less.

12-Spontaneous bleeding. (from gums, nose and gastrointestinal tract.)

13-Hyperparasitaemia of more than 250000 rings/ul.

A questionnaire containing sociodemographic information, clinical examination and investigations was filled for every patient.

Investigations:

Using finger prick blood, thick and thin (if the species were doubted)blood smears were prepared from each patient, stained with Geimsa(PH7.0,diluted in PBS) and the parasite counted against 200 white blood cells (WBCs) assuming that the number of WBCs is 6000/***u***l of blood. The blood films were prepared and examined by highly expert technician and crossed-checked by another technician blinded about the results and verified by a supervisor if there was any controversy.

All patients were staying in the same area during the follow up period. Therefore, the possibility of reinfection or recrudescence was present. Three spots of blood were taken on filter paper initially and later if parasites reappeared microscopically during the follow up period. Primers from 3 polymorphic *P.Falciparum* antigens; merozoite surface protein-1 and 2 (MSP-1 and MSP-2) and glutamate-rich protein (GLURP) were used in polymerase chain reaction (PCR) to differentiate between true recrudescence and re-infection.

Treatment And Follow Up

The patients were randomized in three groups by using three boxes, each box contains five envelopes to prevent the bias. Group 1 treated with quinine sulphate tablets (Elie pharmaceuticals, Khartoum,

Sudan) 10 mg/kg three times daily, group 2 with 10mg/kg twice daily whereas group 3 treated with 15 mg/kg once daily. Duration of treatment is one week for each group. In case of children who can not swollow the drug, the tablet was disolved in water and then given orally. The medicine was given under close supervision of the team, the dose repeated for those who vomited the drug within one hour, if the patient vomited again , the dose was given by intravenous quinine infusion in 5% dextrose slowly over two hours, then it was continued as tablet to complete one week treatment.

All patients were followed up –according to WHO protocol – clinically daily for seven days, then weekly for three weeks, blood films were obtained and examined microscopically to detect parasite clearance time (from start of treatment till first negative film) and reappearance of parasitaemia.

The patients were sensitive to the treatment if after administration of the drug the blood film became negative before day seven and remained negative for the following three weeks. They were considered as early R-1 resistance when the parasite disappeared for at least two consecutive days and reappeared on day seven or day fourteen, while they were considered late R-1 resistance when recrudescence occurred on day twenty one or twenty eight. Patients were considered to have R-2 resistance if parasitaemia never cleared within the first seven days, but was reduced to 25% or less of parasitaemia level during the first 48 hours of the treatment. R-3 resistance grade patients reduce

parasitaemia level by less than 75% during the first 48 hours of the treatment or it continue to rise.

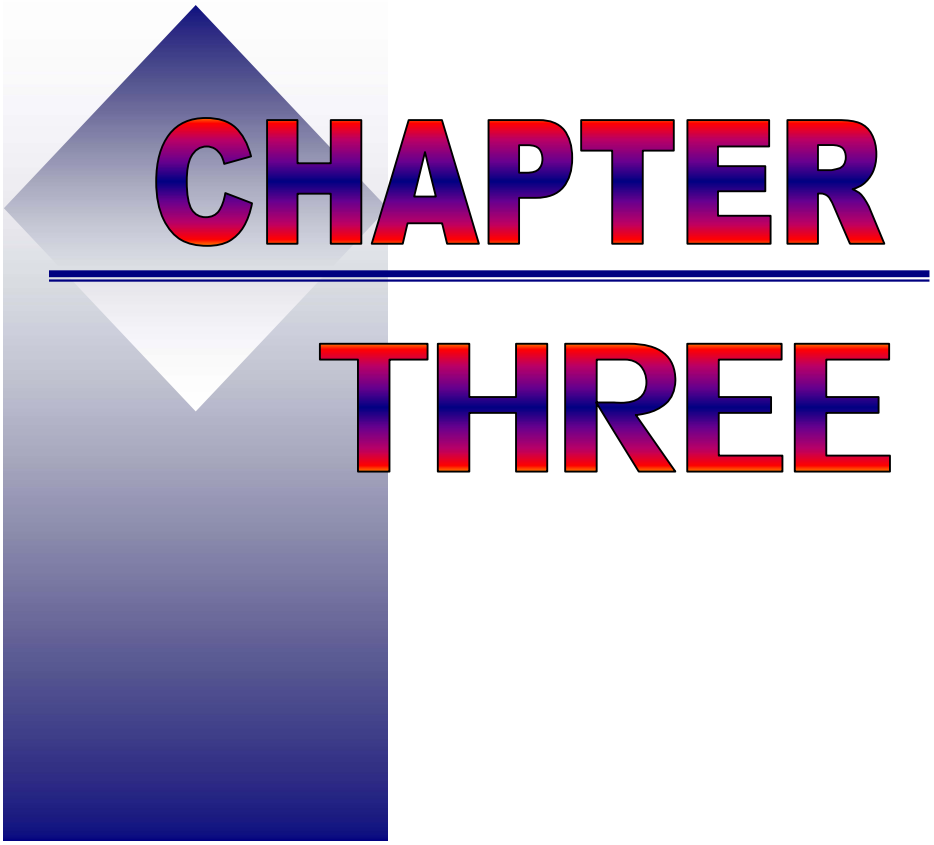
During the follow up period, all patients were asked about recurrence of symptoms, adverse drug reactions and informed not to take any other medication without consulting the team. Patients who failed to take the drug for two days were withdrawn from the study, resistant cases were treated by an alternative drug. The medicine was supplied to all patients free of charge.

Statistical Analysis

Data was entered into a computer database. SPSS software was used for statistical analysis. Differences in percentage of resistance and side effects were compared between the first, second and the third group using X^2 test. The differences in the mean age, weight, initial parasitaemia, the mean temperature and mean parasite clearance time (in days) were calculated by ANOVA one-way analysis. $P < 0.05$ was regarded significant.

Ethical clearance

The study received ethical clearance from the faculty research board at the Faculty of Medicine, University of Khartoum.


CHAPTER
THREE

Results

During the follow up period, 720 patients presented to the primary health centre with symptoms suggestive of malaria, 400 (56%) have positive blood films for malaria,12 patients have severe malaria, 98 patients presented with falciparum malaria after chloroquine failure. Ninety three fulfilled our selection criteria and completed the 28 days follow up, 32, 31 and 30 were assigned to group 1, 2 and 3 respectively. Five patients; 2 in group 1, 1 in group 2, and 2 in group 3 were lost during the follow up period because they changed their addresses.

The mean age is 16.34 years in group 1, 16.69 years in group 2 and 15,93 years in group 3(P=>0.05).

The mean weight is 29.32kg in group 1, 34.54kg in group 2 and 33.66kg in group 3(P=>0.05).

The mean temperature is 38.28C in group 1, 37.98C in group 2 and 38.38C in group 3 (P=>0.05).

The mean parasite clearance time(PCT) is 2.8 days in group 1, 3.1 days in group 2 and 2.8 days in group 3 (P=>0.05).

Due to intractable vomiting the initial quinine dose was given parenterally in 1/32(3.1%), 4/31(12.9%) and 4/30 (13.3%) patients in group 1, 2 and 3, respectively (the difference was not statistically significant).

The number of children is 7(21.9%) in group 1, 5 (16.1%) in group 2, and 6 (20%) in group 3.

The number of males is 23 (71.9%) in group 1, 14 (45.2%) in group 2 and 13(43.3%) in group 3,whereas the number of females is 9 (28.1%) in group1, 17 (54.8%) in group 2 and 17 (56.7%)in group 3 (Table 1).

The number of patients presented with fever is 31 (96.9%) in group 1, 30 (96.8%) in group 2 and 29 (96.7%) in group 3 (Table 2).

Table 3 showed that headache was recorded in 76.3% of the patients.

Vomiting was recorded in 19(59.4%) in group 1, in 15(48.4%) in group 2 and in 14(46.7%) patients in group 3(Table 4).

Sweating was observed in 13(40.6%) in group 1, in 12(38.7%) in group2 and in 9(30%) patients in group 3(Table 5).

Chills was present in 23(71.9%) in group 1, in 23(74.2%) in group 2 and in 17(56.7%) patients in group 3.

Table 6 showed that spleen was palpable in 12.9% of the patients.

. The number of patients who have fever on day 3 is 7 (21.9%) in group 1, 9 (29%) in group 2 and 11 (36.7%) in group 3 (Table 7).

There was no significant difference in the mean temperature on day 3 between the three groups, but the mean (SD) fever clearance times in days was significantly longer in group 2(BD) in comparison with the other two groups (TDS and Once),3 3.5(2.1) vs. 2.3(1.6)and3.5(2.1)vs.2.2(1.3),$P<0.05$.

. Table 8 showed that tinnitus was recorded in 46.2% of the patients after receiving quinine treatment.

The mean(SD) parasite clearance time was 2.8(0.49) in group 1, 3.1(0.45) in group 2 and 2,8(0.92) in group 3 (Table 9). The difference was not statistically significant (P=>0.05).

The mean parasite count was 8971.87/mm in group 1, 9100/mm in group 2 and 8383.3/mm in group 3.

Parasitaemia was detected during the follow up on day 28 or before in 2(6.3%) in group 1, in 5(16.1%) in group 2 and 5(16.7%) patients in group 3; the difference was not statistically significant (P>0.05). The parasitaemia detected was due to true recrudescence in the first and second group , except for one patient in the second group where it has been shown to be due to re-infection. This re-infection was detected on day 21. Parasitaemia was detected in 5 patients from group 3 during the follow-up; two of them were true recrudescence detected on day 14, one case detected on day 21(re-infection), whereas two patients detected on day 28; one was due to re-infection and the other case was due to true recrudescence.

Table (1) :-

Sex distribution among the three treatment groups

Sex		Groups			Total
		Group I	**Group II**	**Group III**	
Male	Count	23	14	13	50
	%Within the group	71.9%	45.2%	43.3%	53.8%
	% of total	24.7%	15.1%	14.0%	53.8%
female	Count	9	17	17	43
	%Within the group	28.1%	54.8%	56.7%	46.2%
	% of total	9.7%	18.3%	18.3%	46.2%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (2) :-

Fever among the three treatment groups

Fever		Groups			Total
		Group I	**Group** II	**Group** III	
Afebrile	Count	1	1	1	3
	%Within the group	3.1%	3.2%	3.3%	3.2%
	% of total	1.1%	1.1%	1.1%	3.2%
Febrile	Count	31	30	29	90
	%Within the group	96.9%	96.8%	96.7%	96.8%
	% of total	33.3%	32.3%	31.2%	96%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (3) :-

Headache among the three treatment groups

Headache		Groups			Total
		Group I	Group II	Group III	
No headache	Count	6	11	5	22
	%Within the group	18.8%	35.5%	16.7%	23.7%
	% of total	6.5%	11.8%	5.4%	23.7%
Headache	Count	26	20	25	71
	%Within the group	81.3%	64.5%	83.3%	76.3%
	% of total	28.0%	21.5%	26.9%	76.3%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (4) :-

Vomiting among the three treatment groups

Vomiting		Groups			Total
		Group I	Group II	Group III	
No vomiting	Count	13	16	16	45
	%Within the group	40.6%	51.6%	53.3%	48.4%
	% of total	14.0%	17.2%	17.2%	48.4%
Vomiting	Count	19	15	14	48
	%Within the group	59.4%	48.4%	46.7%	51.6%
	% of total	20.4%	16.1%	15.1%	51.6%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (5) :-

Sweating among the three treatment groups

Sweating		**Groups**			**Total**
		Group I	**Group II**	**Group III**	
No sweating	Count	19	19	21	59
	%Within the group	59.4%	61.3%	70.0%	63.4%
	% of total	20.4%	20.4%	22.6%	63.4%
Sweating	Count	13	12	9	34
	%Within the group	40.6%	38.7%	30.0%	36.6%
	% of total	14.0%	12.9%	9.7%	36.6%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (6) :-

Splenomegaly among the three treatment groups

Splenomegaly		Groups			Total
		Group I	Group II	Group III	
No splenomegaly	Count	29	27	25	81
	%Within the group	90.6%	87.1%	83.3%	87.1%
	% of total	31.2%	29.0%	26.9%	87.1%
Splenomegaly	Count	3	4	5	12
	%Within the group	9.4%	12.9%	16.7%	12.9%
	% of total	3.2%	4.3%	5.4%	12.9%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (7) :-

Fever on day 3 among the three treatment groups

Fever on day 3		**Groups**			**Total**
		Group I	**Group II**	**Group III**	
Afebrile	Count	25	22	19	66
	%Within the group	78.1%	71.0%	63.3%	70.7%
	% of total	27.2%	22.8%	20.7%	70.7%
Febrile	Count	7	9	11	27
	%Within the group	21.9%	29.0%	36.7%	29.3%
	% of total	7.6%	9.8%	12.0%	29.3%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (8):-

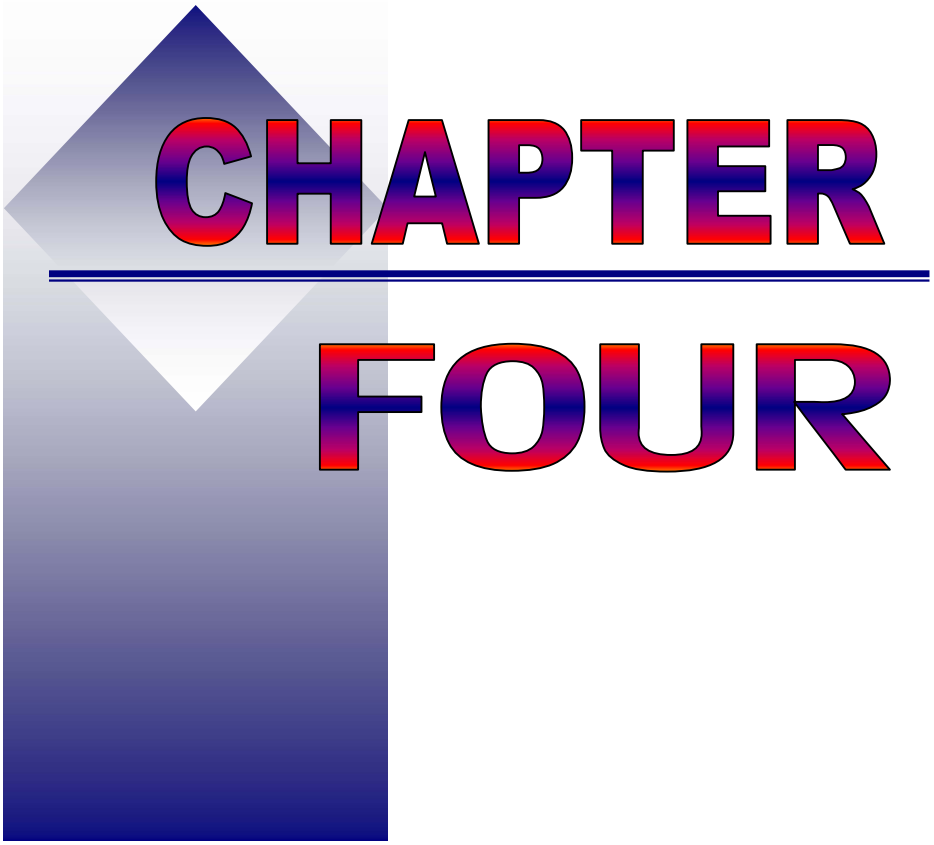
Tinnitus among the three treatment groups

Tinnitus		**Groups**			**Total**
		Group I	**Group II**	**Group III**	
No tinnitus	Count	15	20	15	50
	%Within the group	46.9%	64.5%	50.0%	53.8%
	% of total	16.1%	21.5%	16.1%	53.8%
Tinnitus	Count	17	11	15	43
	%Within the group	53.1%	35.5%	50.0%	46.2%
	% of total	18.3%	11.8%	16.1%	46.2%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%

Table (9) :-

Resistance among the three treatment groups

Resistance		**Groups**			**Total**
		Group I	**Group II**	**Group III**	
Responsive	Count	30	26	25	81
	%Within the group	93.8%	83.9%	83.3	87.1%
	% of total	32.3%	28.0%	26.9%	87.1%
Resistant	Count	2	5	5	12
	%Within the group	6.3%	16.1%	16.7%	12.9%
	% of total	2.2%	5.4%	5.4%	12.9%
Total	Count	32	31	30	93
	%Within the group	100.0%	100.0%	100.0%	100.0%
	% of total	34.4%	33.3%	32.3%	100.0%


CHAPTER
FOUR

Discussion

Our study showed that quinine dose could be reduced effectively, even to single dose per day (15mg/kg), as there was no significant difference in the rate of reappearing of parasitaemia between the three groups. P. Deloran and colleagues –Madagascar- studied the effect of short term oral quinine in treatment falciparum malaria in two different groups treated for different periods and followed up for two weeks. The first group treated for two days whereas the second group treated for three days. Parasitaemia reduced by 97% on day 14 in group two and was more than six times lower than that in group one [60].In that study the follow up period was relatively short, and some cases of true recrudescence might not be detected during this period. In our study most cases of re-infections and recrudescence occurred after day 14, also in this study the duration of the treatment was shorter than in our study, and the duration of the treatment and the total daily dose were different in the two groups ; these factors make the comparison difficult.

Kofoed et al. studied the effect of different doses of quinine in Guinea-Bissau in children treated for seven days. This study indicated that treatment of non severe falciparum malaria with single daily dose of 15mg quinine salt/kg is sufficient. Apparently pre-existing immunity has contributed to the clearance of parasite; antimalarial-drugs are more effective in semi-immune subjects than in non immune, as the patient's immune system adds to the effect of the

drug[61]. No significant differences were found between the quinine concentration in the blood in children who had and children who did not have recurrent parasitaemia in any of the treatment groups, indicating that the length of treatment is more important than the doses ,however, the drug concentrations were significantly higher in group 1 than in group 2 and group 3, but also in group 2 as compared to group 3[62]. It has generally been assumed that antimalarial blood concentrations should remain within the therapeutic range throughout the dosing interval [63].This view has, however, been challenged by observation that once-daily adminstration of artemisinin derivatives, which have elimination half lives of <1 hour, is not associated with inferior immediate responses compared to more ferequent adminstration [63].

These findings are consistent with our study, however, this comparison should be taken cautiously; firstly, the difference in the transmission rate in different locations should be noted, for example, in Kenya anti malarial treatment failures were found to be 9.5% and 34.5% in two different areas at the same time. The difference was attributed to the variation in the endemicity, hence the greater drug selection preassure [64]. Secondly in this study quinine was assessed in all age groups while in Guinea-Bissau quinine was assessed in children who are more likely to have greater parasite resistance to antimalarials

than the other groups [65]. Thirdly, in this study quinine was used for the treatment of chloroquine resistant falciparum malaria, whereas in the previous study patients were excluded if chloroquine was used. However, antagonism between chloroquine and quinine was previously postulated [66,63].

Christophe et al. compared the efficacy of three and seven days oral regimen of quinine in treatment of uncomplicated falciparum malaria in Senegal.

The probability of being free of parasiitaemia was higher among the older children regardless of the treatment group increasing by a factor of 1.6 per year of age indicating the impact of immunity on parasitological clearance time. Parasitaemia detected on day 28 or before was 48% in group 1 and 47% in group 2 [67].

In this study the duration of the treatment was different between the two groups, but the total daily dose of quinine was equal, however, in our study the duration of the treatment was equal in all the groups, but the total daily dose was different. The percentage of parasitaemia detected during the follow up period in each group in this study was higher than that in our study.

Kofoed et al. compared the effectiveness of three regimens of quinine in treatment of children with ***P. falciparum*** malaria in Ginea-Bissau. They divided the children 3 groups, treated for 3,5 and 7 days and received equal doses of quinine.

During the follow up period, the lowest percentage of children who had parasitaemia was detected in the 7 day treatment group[68] . Again this study demonstrates the influence of the length of quinine treatment period on recrudescence and re – infection rates.

Kofoed and colleagues compared different doses of quinine for treatment of falciparum malaria in 3 treatment groups of children treated for 7 days in Guinea-Bissau. The lowest percentage of children who have parasitaemia was found in the group which was treated by the highest daily dose of quinine [69]. This clearly demonstrated the importance of the quinine dose as well as duration of the treatment in treatment of falciparum malaria.

Studies invitro using continuous culture of P.falciparum of the parasite population survives exposure to extremely high quinine concentration for up to 96 hours, while at low concentration of quinine similar to those obtained invivo, no live parasites were seen following 168 hors of exposure, indicating that the period of treatment is very important [70].

The reduced quinine dose in this study was found effective in clearing parasitaemia without any significant difference in

reappearing of parasitaemia. Natural protective immunity may have been responsible for the absence of a difference between the treatment groups. Quinine is the second most prescribed ant-malarial drug in Sudan [71] , and the wide –spread use of insufficient dosage is likely to enhance the development of black water fever and quinine –resistant plasmodium falciparum strains, which have already been reported in some african countries [72]. A previous study carried in the same area – New Halfa- showed that 9.6% of the patients infected with plasmodium falciparum were resistant to quinine [9] .

Conclusion

In conclusion, a single daily dose with 15 mg quinine/kg. for 7 days can be used in treatment of chloroquine resistant falciparum malaria in Sudan. We believe that this recommendation is valid for all age groups and probably also for other parts of Africa where quinine resistance is not suspected.

Giving a single dose of 15mg.quinine/kg. for 7 days did not increase the level of severe adverse drug effects significantly although the risk should be considered in future studies.

Recommendations

According to the results of this study, I recommend the use of single daily dose of 15 mg. quinine/kg. for 7 days for treatment of chloroquine resistant falciparum malaria in Sudan.

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APPENDIX

Questionnaire

Date: ……

Name: …….

Age: ……

Sex: …….

Address: ……..

Nearest person to contact: …….

Last dose of chloroquine: …….

Symptom:

Fever	yes ☐	no ☐
Headache	yes ☐	no ☐
Vomiting	yes ☐	no ☐
Nausea	yes ☐	no ☐
Sweating	yes ☐	no ☐
Chills	yes ☐	no ☐
Backache	yes ☐	no ☐
Diarrhoea	yes ☐	no ☐
Abdominal pain	yes ☐	no ☐
Itching	yes ☐	no ☐
Cough	yes ☐	no ☐
Insomnia	yes ☐	no ☐
Others	yes ☐	no ☐

Examination:

Weight: ……

Temperature: ……..

Pulse: ……..

Blood pressure: …….

Respiratory rate: ……

Pallor: ……

Jaundice: ……

CVS: ……..

Chest: …….

Abdomen:

- Liver: ……
- Spleen: …….

Investigations:

BFFM: …….

Hb: ……

Parasite count: …….

Treatment:

Quinine

Dose:……

Oral: ……..

Intravenous: ……

Follow up chart:

Variable	days									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**21**	**28**
Headache										
Vomiting										
Abd. Pain										
Backache										
Insomnia										
Giddiness										
Itching										
Tinnitus										
Temp.										
Liver										
Spleen										
BFFM										
Parasitaemia										

Temperature clearance time: ……

Parasite clearance time: ……..