Drug Treatment of Falciparum Malaria

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เรื่องย่อ

ยารักษามาลาเรียชนิด *P. falciparum*

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มาลาเรียยังเป็นปัญหาสำคัญ และก่อโรคในประชากรทั่วโลกประมาณ 300 ล้านคน มาลาเรียชนิด *P. falciparum* ก่อโรคได้รุนแรงที่สุด และทำให้ผู้ป่วยถึงแก่กรรมได้มากกว่าชนิดอื่น นอกจากนี้ยังเป็นเชื้อที่ดื้อยาได้หลายขนาน ยาคลอโรควินใช้รักษาผู้ป่วยที่เกิดจากเชื้อชนิดนี้ในประเทศไทยไม่ได้ผล ส่วนยา amodiaquine มีพิษทำให้เกิด agranulocytosis จึงไม่นิยมใช้ ยากลุ่ม sulfadoxine/pyrimethamine เคยใช้ได้ผลดีในอดีตแต่ปัจจุบันใช้ไม่ได้ผลเลยในประเทศไทย ยาควินินยังใช้ได้ผลกับมาลาเรียชนิด *P. falciparum* ถ้าหากนำมาใช้ร่วมกับยาเตตร้าศัยคลินได้ผลถึงร้อยละ 90 ถึงแม้จะมีเชื้อดื้อยาเกิดขึ้นบ้าง ยากลุ่มควินิดินใช้รักษาได้ผลดีเท่ากับควินิน ส่วนยาใหม่ เช่น mefloquine ใช้รักษามาลาเรีย *P. falciparum* ได้ผลราวร้อยละ 71 ถึงร้อยละ 81 ถ้าใช้ขนาด 25 มก./กก. ยากลุ่ม halofantrine เป็นยาใหม่แต่ได้ผลในการรักษาเพียงร้อยละ 58-70 เท่านั้น ยาใหม่ขนานอื่นที่ได้รับการกล่าวถึงบ่อยในขณะนี้คือ อนุพันธ์ของสาร artemisinin อนุพันธ์ที่ได้รับการขึ้นทะเบียนยาให้นำมาใช้รักษาผู้ป่วยได้แล้วในประเทศไทยขณะนี้คือ artesunate และ artemether เป็นยาที่ให้ผลการรักษาร้อยละ 88 และผลการรักษาจะเพิ่มขึ้นถึงร้อยละ 100 ถ้าให้ร่วมกับ mefloquine ขนาดของยาที่ใช้รักษามาลาเรียและข้อควรระวังได้แสดงไว้ที่ท้ายบทความนี้แล้ว *(วารสารโรคติดเชื้อและยาต้านจุลชีพ 2537 ; 11 : 89-93.)*

Key words: Malaria, Multi-resistant falciparum malaria, quinine, mefloquine, halofantrine, artemisinin, artesunate, artemether

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Malaria remains a major health problem in developing countries. It has been estimated that over 300 millions people are infected and over two million, especially children under one year of age, die each year from the disease. Of the four species of human malaria, infection with *P. falciparum* is the most serious and life-threatening to man. Although the life cycle of the malaria parasite has been discribed for 100 years, eradication of malaria has still not been achieved. There are several major difficulties. Malaria vaccine development has been carried on for 30 years without promise of success in the near future. Vector control has been

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Received for publication: September 16, 1993

complicated by resistance to insecticides. Above all, *P. falciparum* is becoming progressively more resistant to all available antimalarial drugs. This article deals with the present situation of the treatment of multidrug resistant falciparum malaria, with special reference to Thailand.

Chloroquine

Chloroquine was the first synthetic antimalaria introduced about fifty years ago, and for many years was the mainstay of antimalarial treatment for all four human malarias. Because of increasing chloroquine resistance in most of the malaria endemic areas in recent years, chloroquine can only be recommended at present for treating non-immunes with *P. falciparum* infections acquired in some parts of West Africa and Central America. In Thailand, the cure rate of chloroquine reached 0% in 1986 and it has not been used for treatment since then (1). However, chloroquine is still the drug of choice in the treatment of *P. vivax, P. malariae,* and *P. ovale* infections.

Amodiaquine

Amodiaquine is similar to chloroquine and was once used as a substitute for chloroquine. However, the potential toxicity of amodiaquine leading to agranulocytosis limits the use of amodiaquine for the treatment of malaria (2).

Sulfadoxine/Pyrimethamine

The combination of pyrimethamine (dihydrofolate reductase inhibitor) with sulfadoxine (PABA inhibitor) has been shown to potentiate antimalarial activity and produces radical cure of malaria infections. This combination was effective when it was first introduced as a single dose treatment for acute uncomplicated falciparum malaria (3). Over the years, resistance has developed in many parts of the world. Increasing failure rates are reported from Columbia, Brazil, Venezuela, Indonesia, Malaysia, Papua New Guinea, Kenya, Burma, and Thailand (1, 4, 5). In some parts of Thailand, it is totally ineffective.

Quinine

Quinine is the most commonly used and available drug in treating falciparum malaria. Recently its effectiveness has declined when is used alone. Increased quinine resistance is appearing in several parts of the world including Tanzania, Vietnam and Thailand (1, 4); however, most of the resistance is at the RI level (clearance of asexual parasitaemia within 7 days of initial of treatment, followed by recrudescence (5)). Minimal inhibitory concentrations (MIC) of quinine for *P. falciparum* parasites have risen above 10 mg/L in some areas. In this situation and in severe malaria, a loading dose of 20 mg of quinine dihydrochloride per kg body weight and maintenance doses of 10 mg per kg given every 8 hours are required (6). Persistent parasitaemias after a loading dose of quinine treatment are not uncommon (7). It is believed that the MIC of quinine must be maintained for seven days to effect radical cure of *P. falciparum* infections. Therefore, quinine must be given for at least seven days or longer (8, 9). In quinine-resistant areas, a second drug such as tetracycline has been added to increase cure rates which approached 100% in 1986 (1) but have declined in 1991 to 90% (10). In children in whom tetracycline is contraindicated, increasing the dose of quinine to 15 mg/kg in the second half of the treatment period improves the cure rate (9).

Quinidine

Quinidine, the diastereomer of quinine, has a lower MIC for *P. falciparum* in Thailand (11). It is as effective as or perhaps more effective than quinine for the treatment of falciparum malaria, as shown in open trials of oral quinidine sulfate and parenteral quinidine gluconate in acute uncomplicated falciparum and severe malaria patients in Thailand (11-13).

Mefloquine

Mefloquine, a synthetic 4-quinolinemethanol, was developed by the US Army antimalarial drug development program. It was initially thought to be the ideal antimalarial. Its action is rapid and is effective against all species of human malaria parasites, including chloroquine-resistant *P. falciparum*. In an effort to delay development of resistance to mefloquine, a combination of mefloquine and sulfadoxine-pyrimethamine (Fansimef^{R}) was advocated. This drug has been registered for use by this trade name in Thailand since 1984. The evidence that the combination may delay development of drug resistance came mainly from a mouse model (14) and has not been generally accepted. In patients with acute falciparum malaria, the combination did not appear to have retarded the development of resistance (15).

Furthermore, severe adverse effects have resulted presumably from the sulfadoxine component when the combination was used for malaria prophylaxis (16). It now seems unequivocal that mefloquine should be used as a single component. Treatment failures have been reported in many parts of the world due either to true parasite resistance (intrinsic) or inadequate dosing. In Thailand, Fansimef^{R} with mefloquine at 15 mg/kg gave a cure rate of over 98% of uncomplicated falciparum malaria in 1983 to 1986 (17, 18) but was reduced to 71% in 1990 (19). However, a higher dose of mefloquine (25 mg/kg) given in 2 divided doses 6 hours apart, achieved a cure rate of 81% in 1991 (20). In children, mefloquine alone, in doses ranging from 18 to 25 mg/kg, has also shown a decrease in cure rates from 98% in 1986 to 73% in 1990 (19, 21). However, when mefloquine (25 mg/kg) was combined with tetracycline (1 g/day for 7 days) or doxycycline (200 mg/day for 7 days), cure rates were significantly improved, to 94% and 96% respectively.

Halofantrine

Halofantrine, a phenanthrene methanol, is another product of the US Army antimalarial drug development program. It was shown in initial studies to be effective against multidrug resistant *P. falciparum* both in Thailand and Africa (22-25). However, studies in Thailand in 1988 and 1991 showed that halofantrine (total dose of 1,500 mg given in three doses) cured only 58% and 70% of patients even though this drug had not been widely used (26, 27). Higher doses of Halofantrine were tested at different regimens in Thailand showed increase cure rates. However, some electrocardiogram changes were observed in karen patients in the western part of Thailand which required a proper further investigation (28,29). At present, halofantrine is registered for use in the USA at a dose of 8 mg/kg given 8 hourly on day 1 and day 7.

Qinghaosu (artemisinin) derivatives

Qinghaosu is a sesquiterpene lactose peroxide extracted from the qinghao plant (*Artemisia annua* L.) It has been used in Chinese traditional medicine for over 2000 years (30, 31) to treat the chills and fever associated with malaria. The active constituent against malaria, artemisinin, was isolated in 1972. Qinghaosu derivatives are very effective in killing parasites; however, recrudescent rates are high (32-37). Attemps have been made to reduce the high recrudescent rates following treatment by increasing the dosage or lengthening the period of drug administration or using drug combinations. Two derivatives, (artemether and artesunate) are now widely used. Other qinghaosu derivatives including arteether and artelinic acid, are under development. Currently arteether is undergoing phase I clinical trial in the Netherlands and a Phase II clinical trial is being planned for 1994 in Thailand.

Artesunate

Artesunate is formulated either as tablets (50 mg tablet) or as a dry powder of artesunic acid for injection (supplied in 60-mg vial with an ampoule of 5% sodium bicarbonate 1 ml). The powder is dissolved in the sodium bicarbonate and then diluted in 1 ml of normal saline immediately before intravenous or intramuscular injection. Artesunate is manufactured by Guilin No. 2 Pharmaceutical Factory, Guangxi, China. It has rapid antimalarial activity with the clearance of over 90% of parasitaemias in 24 hours after initial treatment (20, 35-37). However, the recrudescence rates are high, ranging from 10 to 30% depending upon the dose and duration of treatment. A recent study in Thailand showed that oral artesunate at a total dose of 600 mg given over 5 days had a cure rate of 88%, but the efficacy was increased to 100% in both acute uncomplicated and recrudescent falciparum malaria infections when mefloquine 1,250 mg (divided in 2 doses 6 hours apart) was given following artesunate treatment (20, 38). If half doses of artesunate followed by 750 mg mefloquine was given over 2.5 days for treatment, the cure rate reduced to 90% (39). Both oral and parenteral preparations of artesunate are licensed for use in Thailand. To reduce the high recrudescent rate, the use of artesunate in combination with other drugs is being investigated in Thailand. The shortest duration of drugs in combination treatment is 2 days with an acceptable cure rate of 92%. This combination regimen is artesunate (Plasmotrim Lactab^{R}) 200 mg given twice a day for 2 days followed by mefloquine (Mephaquin Lactab^{R}) 750 mg single dose (40).

Artemether

Artemether (60 mg ampoule), manufactured by Kunming Pharmaceutical Factory, Kunming, China, is formulated in peanut oil for intramuscular injection and licensed for use in Thailand. Oral artemether (tablet and capsule of 50 mg) is undergoing clinical trial. As

with artesunate, the parasiticidal effect is rapid, with clearance of over 90% of parasitaemias in 24 hours after initial treatment (35, 41). Unfortunately, recrudescence rates are high as well. Artemether in combination with other drugs are under study in Myanmar and Thailand (42, 43).

Recommendation for treatment of acute uncomplicated falciparum malaria (in multidrug resistant areas)

1) Quinine 10 mg/kg given 8 hourly for 7 days plus tetracycline 1 gm/day for 7 days. Tetracycline is not recommended in children under 7 years of age. In this situation, the dose of quinine should be increased to 15 mg/kg in the last 4 days of the treatment course.

2) Quinidine 10 mg salt/kg given 8 hourly for 7 days.

3) Mefloquine 25 mg/kg divided into 2 doses, 15 mg/kg given initially and 10 mg/kg 6 hours apart.

4) Halofantrine 8 mg/kg given 8 hourly for 2-3 days.

5) Artesunate 1.2 mg/kg given 12 hourly for 5-7 days.

6) Artemether 1.2 mg/kg given 12 hourly for 5-7 days.

7) Sequential administration of artesunate or artemether with the dose as mentioned in 5 and 6 followed by mefloquine with the dose as mentioned in 3 ; this sequential treatment gives a 100% cure rate (20, 38). The short course of this sequential treatment is artesunate (4 mg/kg) twice a day for 2 days followed by mefloquine (15 mg/kg) single dose (40)

Important points

1) Parenteral antimalarial drugs should be administered in patients with severe infections and in those whose condition deteriorates after being treated with oral preparations. Severe malaria may be complicated by coma, pulmonary oedema, acute renal failure, hypoglycemia, lactic acidosis, liver dysfunction, anaemia, intravascular haemolysis, and concurrent systemic bacterial infections. Supportive treatment of these complications is essential to reduce mortality.

2) Recurrent fever during the first two months after treatment for malaria should be reinvestigated. Treatment failures can occur in any treatment regimens as falciparum malaria is becoming progressively more resistant to all existing drugs. In addition, mixed infection with *P. vivax* occurs in about one-third of patients which becomes manifest within two months after being treated for falciparum malaria (44).

3) Malaria patients may have other diseases which they contract in the malarious areas (e.g. scrub typhus, filariasis, amoebiasis, leptospirosis, typhoid etc.). If fever persists after treatment of malaria, other causes of infection should be sought.

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