ANTIMALARIAL DRUG EVALUATIONS: NAMRU-2 AND INDONESIAN PARTNERSHIP

WJR Taylor*, Thomas L. Richie*, Emiliana Tjitra**

ABSTRAK

EVALUASI OBAT ANTIMALARIA: KEMITRAAN NAMRU-2 DAN INDONESIA

Meningkatnya insiden malaria di beberapa daerah tertentu terutama di Indonesia Bagian Timur disebabkan antara lain : P. falciparum *telah resisten terhadap beberapa obat antimalaria, ditemukannya* P. vivax *resisten klorokuin, dan belum tersedianya vaksin yang efektif. Sehubungan dengan hal tersebut, dilakukanlah evaluasi obat antimalaria yang perlu dipertimbangkan dalam peningkatan pelaksanaan program.*

Obat antimalaria meflokuin, halofantrin dan beberapa derivat qinghaosu (artesunat dan artemeter) telah diuji coba klinik di Indonesia, dan memberikan efikasi yang cukup baik walaupun perlu dipertimbangkan kemungkinan efek samping dan resistensi atau rekrudesensi yang mungkin terjadi serta harganya yang relatif masih mahal.

Obat antimalaria baru yang direncanakan akan diuji coba klinik adalah azithromycin, derivat primaquine WR 238605, atovaquone dan derivat qinghaosu lain.

Dasar pengembangan pengobatan malaria adalah sebagai berikut :

1. *Meningkatkan atau memperbaiki efikasi pengobatan malaria tanpa komplikasi yaitu dengan mengembangkan kombinasi atau regimen obat antimalaria yang tersedia di Indonesia (klorokuin dan tetrasiklin/doksisiklin) atau dengan mempersiapkan obat antimalaria baru (derivat qinghaosu, atovaquone, azithromycin dan WR 238605).*
2. *Mencari obat antimalaria baru alternatif yang efektif sebagai obat penyelamat untuk pengobatan malaria dengan komplikasi.*

Dengan melakukan evaluasi obat antimalaria ini, akan didapat data efikasi dan keamanan yang dapat membantu Departemen Kesehatan untuk menentukan obat pilihan di Indonesia. Selain itu juga dapat ikut membantu menanggulangi masalah malaria di dunia.

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* U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia

** Communicable Diseases Research Centre, NIHRD, Ministry of Health, Jakarta, Indonesia.

INTRODUCTION

The Naval Medical Research Unit Number 2 (NAMRU-2) throughout its twenty five year history has worked closely with several Indonesian institutions and the Ministry of Health to carry out malaria research in different parts of Indonesia. These institutions include: the Center for Health Research and Development (Badan Litbangkes), the Center for Disease Control and various Provincial Health Authorities. This article will outline the antimalarial drug evaluation program being considered between NAMRU-2 and the Indonesian Ministry of Health.

Recent evidence suggests that malaria incidence is increasing in certain parts of Indonesia but is particularly problematic in the eastern parts of the country where antimalarial drug resistance has been recognized for some time for *P. falciparum*[1-4]. In Irian Jaya (also in adjacent Papua New Guinea) and in Nias, northern Sumatera, there is strong evidence that chloroquine resistant *P. vivax* is contributing to the malaria problem[5-9].

CURRENT EXPERIENCE WITH ANTI-MALARIAL DRUGS IN INDONESIA

The current medications for treatment of malaria blood stage infection approved for use in Indonesia are chloroquine, pyrimethamine/sulfadoxine (Fansidar®), and quinine, with primaquine approved for treatment of liver stages of *P. vivax* and sexual stages of *P falciparum*. Mefloquine, halofantrine and artemether have been evaluated in limited trials (see Table 1 and Table 2) but are not currently approved for widespread use. Each of these agents is associated with one or another problem related to toxicity or resistance.

Chloroquine resistance is high and widespread throughout the archipelago but concentrated in the east. Combination therapy with primaquine may overcome some of the resistance seen in *P. vivax* (K. Baird, personal communication) but this regimen must be completely evaluated and the problem of quick, inexpensive and accurate G6PD testing, recommended for the use of primaquine, remains to be solved. Fansidar® resistance is also common[3,10] and the treatment is occasionally associated with the Stevens-Johnson syndrome in those individuals with sulfa drug sensitivity. Quinine, while effective, has side effects that make it unpalatable to many patients, resulting in poor compliance and subsequent treatment failure. Quinine resistance is increasingly reported in SE Asia.

Anecdotal reports of mefloquine prophylaxis failures in eastern Indonesia and of in vitro resistance (K. Baird, personal communication and[11-12]) are worrisome and suggest that its utility and that of the related compound, halofantrine, may be short-lived. Mefloquine has been associated with several cases of acute psychosis as well as vertigo and sleep disturbances that make it intolerable for some patients. Halofantrine, given as a three dose regimen over 12 hours, is effective against most strains of falciparum malaria; however, non-immunes often require a second course of treatment, as evidenced by the recrudescent parasitemia seen in patients treated with halofantrine in Indonesia[13-14]. Halofantrine has poor bioavailability. It causes significant lengthening of the QT interval of the ECG which has lead to a few cardiac deaths in predisposed persons. In addition, malaria strains resistant to mefloquine are often also resistant to halofantrine, causing the drug to be of limited usefulness for treating *P. falciparum* in areas where mefloquine resistance has developed.

Table 1: Prophylaxis

Summary of currently licensed and unlicensed antimalarial prophylactic drugs and their efficacy in RI.

DRUG	APPROVAL STATUS				REMARKS		
	MALARIA		OTHER[1]		ADVANTAGES	DISADVANTAGES	COST / WEEK[6]
	RI	USA	RI	USA			
Weekly chloroquine (300 mg base)	Yes	Yes	Yes	Yes	widely available; can be used in pregnancy, breast feeding & children; cheap	poor efficacy[4]; unsuitable in epilepsy, opthalmic toxicity, regular opthalmic review may be needed for long-term use	Rp. 200
Weekly mefloquine (250 mg)	No	Yes	No	No	excellent efficacy[4]	rare CNS & cardiac toxicity, contraindicated in pregnancy & breast feeding, children < 15kg; expensive	6.000
Weekly pyrimeth-amine/sulfadoxine (25 mg/500 mg)	No	Yes	No	No	moderate efficacy; cheap	Stevens Johnson syndrome, bone marrow depression, contraindicated in pregnancy & breast feeding of G6PD deficient infants	600
Daily doxycycline (100 mg)	No	Yes	Yes	Yes	excellent efficacy[4]	contraindicated in pregnancy & children < 8	2.250
Daily primaquine (30 base)	No[2]	No[3]	No	No	good efficacy[4]; widely available; moderate price	contraindicated in pregnancy & G6PD deficiency	1.400
Daily azithromycin (250 mg)	No	No	Yes	Yes	promising efficacy[5], well tolerated; can be used in children, probable use in pregnancy/ breast feeding	expensive	45.000

1. Approved for indications other than malaria prophylaxis or treatment.
2. Approval for treatment of liver stages of *P. vivax* (radical cure) and treatment of sexual stages (gametocytes) of *P. falciparum*.
3. Approval for treatment of liver stages of *P. vivax* (radical cure).
4. Studies by NAMRU in Irian Jaya.
5. Not yet tested in Indonesia for antimalarial prophylaxis. Clinical trial planned.
6. Adult dose; source: IIMS (Indonesia Index of Medical Specialties, 1995), except mefloquine (British National Formulary, 199).

Table 2: Treatment: Summary of currently licensed & unlicensed drugs used for the treatment of malaria and their efficacy in RI.

DRUG	APPROVAL STATUS				REMARKS		
	MALARIA		OTHER[1]		ADVANTAGES	DISADVANTAGES	Cost / course Rupiah
	RI	USA	RI	USA			
Chloroquine =CQ (600 d1 d2, 300 mg d3	Yes	Yes	Yes	Yes	cheap, widely available, used in pregnancy, breast feeding , children	falciparum resistance widespread[2,3], vivax resistance in Irian Jaya[2] & Nias[2]	500
CQ + prima-quine (60 mg base X 3d)	Yes	No	No (prima quine)	No (prima quine)	improved efficacy against vivax over chloroquine alone[2]	primaquine contraindicated in G6PD deficiency, breast feeding & pregnancy	1.700
CQ + doxy[5] (100mg/12hx7d)	No	No	Yes (doxy)	Yes (doxy)	improved efficacy over chloroquine alone in Africa	efficacy unknown in Indonesia[4], doxycycline contraindicated in breast feeding, pregnancy & children < 8	3.300
Quinine (600 mg/8 hr x 7d)	Yes	Yes	Yes	Yes	good efficacy, rapidly acting	poorly tolerated, poor compliance	6.300
Quinine (X 4d) + doxycycline (x 10d)	No	No	No	No	excellent efficacy[2]	better tolerated than quinine alone for 7 days but still with poor compliance, quinine contraindicated in optic neuritis, tinnitus, hemoglobinuria, pregnancy but benefit of treatment outweighs risk	7.600
Mefloquine (1250 mg)	No	Yes	No	No	good efficacy	expensive, rare CNS & cardiac toxicity, contraindicated in pregnancy, breast feeding, children < 15kg.	36.000
Halofantrine (500 mg/6 hr X 3)	No	Yes	No	No	good efficacy, well tolerated[2,3]	expensive, must be taken on empty stomach, rare cardiac toxicity (deaths), contraindicated in pregnancy, breast feeding, cardiac disease associated with a prolonged QT interval, children < 10kg	23.100
P/S[6] (75 mg / 1500 mg)	Yes	Yes	No	No	moderate efficacy	Stevens Johnson syndrome, bone marrow depression, contra-indicated in pregnancy & breast feeding of G6PD deficient infants	2.520
Artemisinin & derivatives	No	No	No	No	good efficacy[3], rapidly acting, well tolerated	significant recrudescence when used alone, severe neurotoxicity in primates with higher doses	7.000
Atovaquone + Proguanil (500 mg/1 mg X 3d)	No	No	No	Yes (atova-quone)	excellent efficacy against falciparum, well tolerated, proguanil safe in pregnancy	efficacy unknown in Indonesia; atovaquone: limited data on use in pregnancy but may be safe; expensive	81.000

1. Approved for indications other than malaria prophylaxis or treatment (doses, formulations may differ).
2. Studies by NAMRU in Irian Jaya.
3. Studies by LITBANGKES.
4. Not yet tested in Indonesia for antimalarial treatment. Clinical trial planned.
5. Doxcycycline
6. Pyrimethamine/sulfadoxine

Preliminary studies using artemether and artesunate indicate that, as in other parts of the world, there is a significant rate of recrudescence following initial parasite clearance[15-16]. In addition, neurotoxicity has been documented in rats, dogs and monkeys receiving artemether and arteether, raising the possibility that repeated dosing in humans could cause brain stem injury[17-18]. For this reason, development of artemisinin derivatives such as artemether is concentrating on their value for treating severe, life-threatening *P falciparum* infections.

DRUG DEVELOPMENT

Because of emerging drug resistance problems, toxicity of available agents and the lack of an efficacious vaccine on the horizon, Indonesia has reason to be on the cutting edge of antimalarial drug evaluations. For the same reasons, the US Navy and NAMRU-2 would like to evaluate antimalarial drugs in areas of known drug resistance in Indonesia once those agents have been evaluated for safety of use in human subjects. A well developed program of antimalarial drug development will be of great use to the Indonesian Center for Disease Control in mapping resistance patterns throughout the archipelago; and in making recommendations for prevention and treatment.

The US Navy's antimalarial drug development program is closely coordinated with that of the US Army. Antimalarial drugs are discovered and developed largely through a cooperative research program involving the Walter Reed Army Institute of Research (WRAIR), the World Health Organization (WHO) and various pharmaceutical firms (Roche, SmithKline Beecham, Burroughs Wellcome). WRAIR has conducted one of the largest drug screening programs in the world having processed nearly 300,000 compounds searching for antimalarial activity. Drugs developed by the WRAIR/WHO program to address the growing problem of multi-drug resistant *P. falciparum* malaria include mefloquine and halofantrine. Drugs currently under development include the antibiotic azithromycin, the artemisinin (qinghoasu) derivative arteether, the anti-protozoal agent atovaquone, and the as yet unnamed primaquine derivative WR238605.

Compounds under development as antimalarials are extensively screened for toxicity prior to evaluation in the field. Of the four compounds listed above, azithromycin and atovaquone are licensed in the United States for non-malarial indications, so that the usual preclinical and Phase I safety data have been supplemented by extensive experience in the public sector. Unlicensed compounds such as arteether and WR238605 are tested for safety prior to any consideration of field trials. Following animals studies, this initial human volunteer testing takes place in the United States, primarily in US soldiers at Fort Detrick, Maryland. Once the compound is known to be safe and effective in mosquito challenge trials in soldiers, it is ready for efficacy studies where the disease occurs naturally. The US military overseas laboratories and WHO collaborators develop field trials to demonstrate the drug's actual utility in the treatment or prophylaxis of malaria. The best field-applicable drug regimen is defined through testing in more than 1000 individuals in several different sites world-wide. Then pharmaceutical firms become involved in the formulation and mass production of the new antimalarial drug for the world market.

Continual drug discovery and development is necessary due to the rapid development of drug resistance. Malaria parasites are able to

devise metabolic means of escaping drug killing through the progressive selection of increasingly drug tolerant strains. In Thailand, the average useful life time of a new antimalarial drug is 5 to 10 years. Spread of resistant strains from one part of the world to another occurs rapidly through international travel by students, soldiers, refugees and other persons carrying malaria parasites into areas with receptive mosquitoes. Wise drug use policies in one area can be overturned quickly when new drug resistant parasites are introduced from other areas.

The use of new antimalarials has caused concern in Indonesia in the past because of the cost of some of these agents. These drugs are not commercially attractive due to the expense of development ($US 100 to 200 million) and the relatively small returns expected on this investment. Without the involvement of the US Department of Defense and the WHO, it is unlikely that any new drugs would be developed against malaria due to lack of financial incentives. However, through participation in clinical drug trials, countries such as Indonesia can ensure that drugs work against their particular strains of malaria and gain early access to new products usually on favorable terms negotiated with the pharmaceutical developer.

FUTURE PLANS

New drugs expected in the future include the compounds summarized below. NAMRU and Badan Litbangkes plan to evaluate an inexpensive combination of chloroquine and doxycycline that obviates the problem of G6PD testing and uses products already approved in Indonesia. It is hoped that this trial will be followed by the antibiotic azithromycin for prophylaxis and WR238605 for prophylaxis and/or radical cure of incubating tissue infections. Also under consideration is the highly promising combination of atovaquone-proguanil for treatment. Azithromycin is already licensed for use in Indonesia, Europe and the United States and atovaquone and proguanil are licensed as individual agents (not as a combination) in Europe and the United States. Azithromycin and atovaquone are widely used to treat other infections and have been found to be safe. Proguanil is probably the safest of all the antimalarial drugs currently in use and like chloroquine can be given to pregnant women and infants.

1. Tetracycline and doxycycline appear to have significantly improved the efficacy of quinine in Thailand[19-20]. The emergence of chloroquine resistant *P. vivax* in Irian Jaya presents a treatment problem. Fansidar works poorly for *P vivax* and quinine is not well tolerated. It has been observed that private physicians are treating malaria in Irian Jaya with standard chloroquine and 7 days of doxycycline or tetracycline. It is proposed that patients with uncomplicated *P. falciparum* and *P. vivax* malaria presenting for treatment or found on screening will be asked to participate in a hospital based trial of doxycycline plus chloroquine if they have no signs or symptoms suggesting severe malaria. All will be randomized to receive standard therapy with chloroquine for three days alone or chloroquine for three days plus doxycycline for seven days or, only for those with low parasitemia, doxycycline alone for seven days. The main objective of this study is to determine if doxycycline significantly improves the efficacy of the standard chloroquine treatment of *P vivax* and *P falciparum* malaria in Irian Jaya. If the combination is shown to be efficacious, dose ranging studies will follow.

2. Azithromycin is a macrolide antibiotic related to erythromycin that is long-acting and has good tissue penetration. It is currently licensed and widely used for bacterial, mycoplasma and chlamydia infections in the US and Europe, with particular application to respiratory illness. It is licensed for use for similar indications in Indonesia. Azithromycin appears to have significant prophylactic activity against falciparum malaria, with evidence of both tissue and blood schizonticidal effects. It is unclear what the optimum regimen should be, but phase II human prophylaxis trials are currently underway in Kenya. Azithromycin's superiority to doxycycline would appear to be its safety in children and pregnant women (its level of safety and tolerance appear to be similar to that of erythromycin). It is hoped that we will be able to evaluate azithromycin's efficacy in Indonesian soldiers in 1996. Azithromycin may also be useful for the empiric therapy of children presenting with fever and respiratory symptoms in malarious areas. Because the drug appears to be effective against both malarial and respiratory illness, it may prove beneficial in areas lacking the capability for laboratory identification of respiratory and protozoal pathogens.

3. WR 238605 is an analogue of primaquine with a very long half life. It is approximately 10 times more effective than primaquine in treating the liver stages of monkey malaria in both radical curative and causal prophylactic modes. WR 238605 is very well tolerated in humans up to at least 600 mg in a single dose. Although no toxicity has been seen in humans, it is expected from animal studies that WR 238605 will cause hemolysis in G6PD deficient individuals and also methemoglobinemia, similar to primaquine. It has recently been tested for causal prophylaxis in a volunteer challenge study at WRAIR and those results are expected soon. WR 238605 will probably replace primaquine as a radical curative drug and will have profound prophylaxis and public health applications. If WR 238605 lives up to its full promise, it is a drug which, when used in combination with an effective vaccine, may permit the eradication of malaria.

4. Atovaquone is a new class of antimalarial drug. It is currently licensed for the treatment of *Pneumocystis* and *Toxoplasma* in AIDS patients, in whom dosages several times those used for malaria are routine. Atovaquone cannot be used alone for malaria due to the rapid evolution of drug resistance. However, it is extraordinarily effective against multi-drug resistant *P. falciparum* when combined with proguanil or tetracycline. Its current regimen is 1000 mg atovaquone and 400 mg proguanil given once a day, for 3 days. Phase III trials are currently underway in Thailand, Zambia and Kenya and will start soon in Brazil. Preliminary results suggest an excellent record of efficacy for treating drug resistant *P. falciparum* malaria. The drug combination also appears to be very safe and well tolerated. However, its expense may limit broad application in Indonesia at the current time and testing is on hold.

5. Development of artemisinin derivatives as standard treatment for uncomplicated malaria is currently held up due to the severe neurotoxicity demonstrated in rats, dogs and monkeys[17-18]. While receiving doses higher than would normally be given for malaria treatment, these animals developed extensive brain stem lesions,

leading to neurological deficits, and, at higher doses, to death. While neurological damage has not been reported in humans, there is concern that repeated treatment, during the course of childhood for example, could lead to brain stem injury. Studies at WRAIR are currently underway to identify which artemisinin derivatives cause this syndrome, whether the chemical structure responsible for the toxicity is linked to antimalarial activity (or whether the two can be separated, permitting the design of non-neurotoxic derivatives), and whether repeated smaller doses has a cumulative toxicity similar to that seen acutely with higher doses. Pending the results of these studies, many experts are recommending that the use of artemisinin derivatives be restricted to the treatment of severe disease, for which it is at least effective as quinine and for which the toxicity risks are overbalanced by the risks presented by malaria itself.

CONCLUSIONS

To summarize, the drug development program is designed with two principal goals. The first is to develop new drugs that will improve efficacy in the treatment of uncomplicated malaria or in the prophylaxis of malaria. Efforts in this direction can be divided into two parts. First, we are searching for novel combinations of drugs currently available in Indonesia. Examples are primaquine + chloroquine to treat chloroquine resistant *P. vivax*, doxycycline + chloroquine to treat both *P. vivax* and *P. falciparum*, and daily primaquine for prophylaxis of both *P vivax* and *P falciparum*. As a second route to this goal, we wish to evaluate new agents that are either approved for antimalarial indications in other countries or currently under development. Three new drugs or drug combinations that appear particularly promising because of good safety records and expectation of high efficacy include azithromycin, WR238605, and atovaquone / proguanil. A second major goal is evaluating new agents for the treatment of severe and complicated disease. Artemisinin derivatives are potentially excellent alternatives to parenteral quinine and are currently under evaluation in northern Sulawesi as life-saving drugs for the treatment of severe malaria.

By evaluating these drugs, first and foremost the Ministry of Health will be in a position to make drug choice recommendations that are based on known efficacy and tolerance data *in Indonesia*. The Center for Disease Control will be positioned to respond wisely to the emergence of epidemics or new patterns of resistance to the antimalarials currently in use. In addition, Indonesia will gain recognition as a committed member of the international community seeking to overcome the problem of malaria.

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