The Use of Artemisinin & its Derivatives as Anti-Malarial Drugs

Report of a Joint CTD/DMP/TDR Informal Consultation

Geneva, 10-12 June 1998

Malaria Unit
Division of Control of Tropical Disease
World Health Organization
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1. INTRODUCTION

Artemisinin and its derivatives, first discovered, tested and marketed in China, produce more rapid resolution of fever and parasitaemia than all known antimalarial agents. Due to these remarkable properties, there are concerns that their uncontrolled and widespread use, particularly as oral formulations, will result in the rapid development of drug resistance. These concerns were reflected in the recommendations made by WHO Informal Consultations in 1993 and 1995 (WHO, 1994; 1996).

Since these recommendations were made, further experience with the use of artemisinin and its derivatives has been obtained. The prevalence of drug-resistant falciparum malaria has increased and national antimalarial drug policies have consequently changed, particularly in Africa south of the Sahara. Sulfadoxine/pyrimethamine replaced chloroquine as the first-line treatment of uncomplicated malaria in Malawi in 1993 and in Botswana, Kenya and South Africa in 1997. This raised difficulties in the choice of the second line drug to be used for failures of sulfadoxine/pyrimethamine therapy since only a limited number of antimalarial drugs are available. For example, amodiaquine was chosen in Malawi because mefloquine was considered to be too expensive and to have an unacceptable potential for adverse reactions; oral quinine was also unacceptable because of patient compliance with the required 7-day regimen. These difficulties are compounded by reports of increasing resistance to sulfadoxine/pyrimethamine in some areas of East Africa where the use of this combination has increased.

The availability of oral formulations of artemisinin drugs would increase the choice of drugs for use in malaria programmes in Africa if (i) they could be made available at an affordable price and (ii) their use would not lead to the early development of resistance. Papua New Guinea also faced with an unacceptable level of chloroquine failures decided in 1997 to change its antimalarial drug policy, pending efficacy trials, to a combination of chloroquine plus sulfadoxine/pyrimethamine as the first-line drug with oral artesunate alone as the second-line, and parenteral or rectal artesunate for the treatment of severe disease (Drs K. Palmer and Allan Schapira, WPRO Mission Report October 1997).

In light of these considerations, an informal consultation on the use of artemisinin and its derivatives as antimalarial drugs was held in Geneva from 10-12 June 1998 to update WHO policies on the use of these drugs. It brought together persons with experience in preclinical and clinical evaluation of drugs, regulatory affairs, and the use of these drugs in malaria control programmes, together with representatives of the International Federation of Pharmaceutical Manufacturers Associations.

Apart from presentations by the participants, the meeting also discussed the working papers and conclusions of a conference on “The rational use of qinghaosu and its derivatives” convened by the International Laveran Foundation and the Marcel Mérieux Foundation, and held in Annecy from 19-22 April 1998. These were kindly provided by

2. **OBJECTIVES OF MEETING**

The objectives of the meeting were to:

(i) review existing WHO recommendations on the role and use of artemisinin and its derivatives in light of contemporary research and operational experiences;

(ii) advise WHO on policy and guidelines for the selection and correct use of artemisinin and its derivatives in different epidemiological situations; and

(iii) define future research and development needs.

3. **CURRENT STATUS**

3.1 **Availability of drug substances and formulations**

China and Viet Nam continue to be the main producers of artemisinin and its derivatives as both drug substances, and formulations either for oral or parenteral use.

The **most widely available** formulations are:

* * *

**Oral Formulations (country of production)**

| Artemisinin tablets (Viet Nam) | 250 mg |
| Artesunate tablets (China and Viet Nam) | 50 mg |
| Artesunate tablets (Switzerland *) | 200 mg |
| Artesunate tablets (France*) | 50 mg |
| Artemether capsules (China) | 40 mg |
| Artemether composite tablets (China) | 50 mg |
| Dihydroartemisinin tablets (China) | 20, 60 and 80 mg |
| * limited registration in endemic countries |

**Parenteral Formulations (country of production)**

(i) Intramuscular administration

| Artemether injection (China and France**) | 80 mg/1 ml ampoule |
| Arteether injection (India) | 150 mg/2 ml ampoule |
| ** also available as 40mg/ampoule for paediatric use. |
(ii) Intravenous or intramuscular administration

Artesunate (China and Viet Nam) 60 mg /1 ml vial

**Suppository Formulations**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Strength</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin (Viet Nam)</td>
<td>100, 200, 300, 400, 500mg</td>
<td>suppository</td>
</tr>
<tr>
<td>Artesunate (China)</td>
<td>100mg</td>
<td>suppository</td>
</tr>
<tr>
<td>Artesunate (Switzerland*** )</td>
<td>200mg</td>
<td>rectocap</td>
</tr>
<tr>
<td>Dihydroartemisinin (China)</td>
<td>80 mg</td>
<td>suppository</td>
</tr>
</tbody>
</table>

*** limited registration in endemic countries

**Drug substances**

Artemisinin, artemether arteether, artesunate and dihydroartemisinin can all be purchased as drug substances from producers in China and artemisinin, artemether and artesunate from Viet Nam.

For details of prices see section 3.5 below.

**Formulations under development**

The following formulations are at an advanced level of development by the pharmaceutical industry and registration for them is being or will be sought in North America and Western Europe as well as malaria endemic countries in the future:

- Co-artemether [artemether plus lumefantrine (= benflumetol)], oral formulation – Novartis Pharma A.G., Basle, Switzerland.
- Dihydroartemisinin, oral formulation – Artecef B.V., Maarssen, The Netherlands.
- Artelinate intravenous injection - Walter Reed Army Institute of Research, Washington, USA.

**3.2 Registration**

Artemisinin and its derivatives are widely registered for use as antimalarial drugs in malaria endemic countries. To date, no formulation has been registered in Europe or North America although intramuscular artemether can be made available in France and Denmark to individually named patients in the case of need.
The process of registration and authorization of use of these drugs has varied according to the state of development of the registration process. In some countries, the decision-making has been based on an assessment of the epidemiological situation in the country.

Some countries such as Bangladesh and the Philippines do not have a problem with multidrug resistant malaria and have, therefore, not registered these drugs and they are not available on the market. Others such as Myanmar and Viet Nam, facing the problems of multidrug resistance and realizing that some populations do not have access to medical practitioners or to public health services, allow artemisinin drugs to be traded by private and public pharmacies and market-sellers in villages.

Thailand was one of the first countries outside China and Viet Nam to register these drugs. It was facing acute problems of multidrug resistance by the early 1990’s, with chloroquine and sulfadoxine/pyrimethamine being totally ineffective, quinine losing its efficacy and failure rates of mefloquine reaching over 50% in certain areas. Drug manufacturers, importers and sellers must be licensed in Thailand and a full and comprehensive dossier including details of preclinical and clinical studies has to be submitted. In the case of the artemisinin derivatives, the submitted dossiers, based on the translation of the Chinese product files, contained minimal scientific and technical details. They did not adequately detail basic data on drug safety or efficacy and did not provide manufacturing data to allow adequate monitoring of product quality. In spite of these shortcomings, the Thai FDA Technical Subcommittee approved the registration of oral artemunate and intramuscular arteether in July 1991 and intravenous artesunate in January 1992, taking into account that (i) data from clinical trials in Thailand and other countries outside China confirmed the efficacy and safety of these compounds and (ii) there was a clinical and humanitarian need in the country for these drugs to treat multidrug resistant falciparum infections. The probational registration was initially for two years and conditional that (i) their use was restricted to governmental sectors, (ii) the drug packages were labelled clearly on the outside “use only in government sectors”, (iii) post-marketing surveillance was carried out and (iv) all batches of imported drug were quality controlled by the Thai FDA. Thailand also registered the use of artesunate rectocaps in early 1998 (see also section 3.10 below).

Registration and approved use is also restricted in Brazil to governmentally approved hospitals but, in contrast to Thailand, only for the treatment of severe malaria.

In spite of previous recommendations, artemisinin derivatives are widely registered and available on the market in Africa south of the Sahara although they are not used in public health. Injectable arteether and oral artesunate, both produced by French-based companies have been respectively registered in 25 and 13 (mainly francophone) countries of Africa. Formulations from China are also available. Although injectable arteether is not formally registered in South Africa, it may be used for individually named patients in the case of need.
The registration process is in different stages of evolution in countries of Africa and could be any of the following:

- **Notification.** This is the simplest process, where the company is only required to inform the registration authorities of its intention to market the drug. Little or no supporting data is required and the company does not need approval from the authorities for marketing.

- **Authorization.** Information on manufacture, quality, animal toxicity and human efficacy and safety is usually demanded although not necessarily evaluated. The company needs authorization to proceed with marketing.

- **Full registration.** This is in principle the procedure applied in industrialized countries but it operates in only a few African countries. One requirement is evidence of human efficacy and safety in the country itself, using clinical trial protocols approved by the regulatory authority. The authority itself undertakes quality assurance testing of the products to supplement data presented by the company seeking registration. This is, however, beyond the capabilities of most African countries and they have to depend on certification provided by the exporting company. The WHO Certification Scheme for the quality of medicinal products circulating in international commerce is a useful way of ensuring the quality of drugs imported by those countries.

Many countries also insist on the exporting company providing a certificate of registration and free sale in the country of origin. These requirements do not, however, ensure the quality of the imported product since exported batches might not necessarily be manufactured under the same conditions as those used locally.

The weak regulatory systems in many countries of the world are one of the greatest obstacles to the correct deployment and rational use of antimalarial drugs, including the artemisinin and its derivatives. Even where regulatory mechanisms are well established, it is probable that the system is by-passed by illegal activities, including the importation of sub-standard and counterfeit drugs.

The most important constraints in controlling the use of artemisinin drugs are:

- lack of policies for the selection of essential drugs, and for drug registration;
- inability to enforce regulations controlling the importation and distribution of drugs;
- lack of scientific data to develop an appropriate national antimalarial drug policy;
- ignorance and lack of cooperation of prescribers on the rational use of antimalarial drugs;
lack of information, education and communication (IEC) materials on appropriate treatment seeking behaviour leading to unnecessary patient demands for these drugs; and

• commercial market forces for making antimalarial drugs more widely available.

3.3 Quality control

Quality assurance control of drugs, i.e. production according to Good Manufacturing Practice (GMP) and subsequent monitoring of quality throughout the distribution chain, is a crucial element to any essential drugs programme. This is an important issue in relation to artemisinin and its derivatives because most of the available formulations are not produced according GMP standards and the use of counterfeit drugs have been reported in some areas. It is, therefore, particularly important that more effort is made to bring existing production facilities of these drugs up to full GMP levels, and that quality assurance systems should be in place. Countries, such as China, Malaysia, Thailand and Viet Nam, have some experience in carrying out quality control tests for artemisinin and its derivatives.

An assessment of the quality of artemisinin and its derivatives can be made by several methods:

- Thin-layer chromatographic (TLC) identifies the parent compound as well as related substances and can provide an approximate estimation of the content of the drug ingredient;

- High Performance Liquid Chromatography (HPLC) coupled to an Ultraviolet (UV) detector allows the accurate quantitation of the parent drug substance but also the relative quantitation of diluents and breakdown products; and

- In vitro dissolution profiles are being established for tablets, capsules and suppository formulations.

WHO is presently involved in developing and evaluating quality specifications of the drug substance and formulations for artemisinin, artemether, arteether, artesunate and dihydroartemisinin that are intended for publication in The International Pharmacopoeia.

WHO has established collaboration for quality control of antimalarial drugs with the University Sains Malaysia, Penang, Malaysia which is accepting samples of any antimalarial drug including the artemisinin drugs but this facility is insufficient and there is need for the establishment of additional international/regional reference centres as well as for the strengthening of national capacities.
3.4 Extent of use in public and private sectors

The extent of the current use of these drugs is illustrated by the following data. The national malaria control programme in Viet Nam distributed between 1991-1998 31.6 million tablets of artemisinin, 10.5 million artesunate tablets and 793 500 vials of injectable artesunate to the public health services in the country. In addition, 7 million artemisinin tablets, 1.5 million artesunate tablets and over 500 000 vials of injectable artesunate were produced each year from 1995 to 1997 by pharmaceutical concerns in the country for sale in the private sector. Although recent data are not available from China, it has been reported that the sales of artesunate tablets rose from 185 000 to 2 545 000 between 1991 and 1995. In Thailand, which does not produce these drugs and where they are only available in the public sector, consumption of artesunate has risen from 2 880 tablets in 1993 to 653 199 tablets in 1997.

In some countries artemisinin and its derivatives are available through the private sector at prices that are much higher than the prices outlined below. Self treatment may be common. A study of drug utilization patterns in seven sentinel sites in Myanmar showed that overall 16% of respondents practised self treatment with artemisinin. This figure reached over 50% in Monghsat in East Shan State near the Thai border. Such situations can lead to under-dosing, inappropriate combination treatments that ultimately lead to treatment failure, risk of severe malaria and excessive cost to patients. They also have the potential to accelerate the development of drug resistance. Studies in Mynamar also showed that even if the artemisinin drugs were prescribed by a physician, only 30% prescribed the correct dose according to national policy guidelines.

3.5 Market prices

The official costs for export FOB (i.e. freight on board) plus cost of delivery from ports of the manufacturing countries are stated to be:

(i) China

*Formulations*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate tablets</td>
<td>US$ 2.00 for box of 12 tablets</td>
</tr>
<tr>
<td>Artesunate dual pack for injection</td>
<td>US$ 4.80 for box of 6 ampoules</td>
</tr>
<tr>
<td>Artemether capsules</td>
<td>US$ 2.00 for blister sheet of 10 capsules</td>
</tr>
<tr>
<td>Artemether in oil for injection</td>
<td>US$ 4.80 for box of 6 ampoules</td>
</tr>
<tr>
<td>Dihydroartemisinin tablets</td>
<td>price not available</td>
</tr>
</tbody>
</table>
Drug substances

Artemisinin US$ 420/kg
Artemether US$ 3 500/kg
Arteether US$ 3 600/kg
These prices are similar to those quoted in 1993.

(ii) Viet Nam

Artesunate tablets US$ 1.70 for 12 tablets
Artemisinin tablets US$ 1.50 for 10 tablets

(iii) France (These formulations are manufactured according to GMP)

Artesunate tablets US$ 6.00 for 12 tablets
Artemether intramuscular injection US$ 11.88 for 6 ampoules containing 80mg
US$ 6.93 for 6 ampoules containing 40mg

(iv) India

Arteether intramuscular injection US$ 5.00 for 6 ampoules containing 150mg

Prices on the free market in China and Viet Nam are similar to the above. Antimalarial drugs are provided free to patients by the national malaria control programme in Viet Nam which buys them from the manufacturers for around US$ 1.00 for 10 tablets of artemisinin, US$ 0.70 for 12 tablets of artesunate and US$ 3.50 for 6 ampoules of injectable artesunate.

However, there are considerable variations in the price in importing countries where market forces influence costs. In Myanmar, intramuscular arteether costs US$7.00 for 6 ampoules, oral arteether US$ 1.50 for 12 capsules, injectable artesunate US$ 3.50 for 6 ampoules and oral artesunate US$ 1.00 for 12 tablets. In Thailand, the official price of artesunate is 13 Baht (US$ 0.30) per tablet compared with the black market price of 2-3 Baht on the Thai-Myanmar border. In contrast, in other countries and areas, parenteral artesunate or arteether may cost in the order of US$ 30 for a treatment course and oral artesunate around US$ 6. Black market costs may be even higher. These costs are similar to those reported in 1993.
3.6 Clinical use of artemisinin and its derivatives

3.6.1 Treatment of uncomplicated malaria

Artemisinin, artemether and artesunate, have been used in China for the treatment of uncomplicated malaria for over 20 years and increasingly in the rest of South-East Asia for the last decade. Oral dihydroartemisinin has been introduced recently but there is considerable less data on this compound (Zhao and Song, 1993; Looareesuwan et al., 1996a). There appears to be no significant differences in efficacy or tolerability between the different derivatives when given at the currently recommended dosages but comparative data are limited.

In general, oral formulations of these drugs are rapidly but incompletely absorbed, and their bioavailability is low (Bethell et al., 1997). There is good evidence that they undergo extensive first-pass metabolism in the liver. Both artesunate and artemether are rapidly transformed into dihydroartemisinin so that the metabolite is generally present at higher levels than the parent compound (Teja-Isavadharm et al., 1996). Although dihydroartemisinin is the most active derivative on a molar basis, each of the parent drugs are active in the low nM range and are known to achieve levels much higher than the minimum inhibitory concentrations in the plasma. In spite of the rapid clearance and extent of transformation, the parent drugs may contribute a significant proportion of the antimalarial effect in the blood (Hien and White, 1993; ter Kuile, et al., 1993).

No pharmacological interactions with other drugs have been identified although there is a theoretical risk that a pharmacodynamic interaction with desferoxamine might attenuate antimalarial activity (Looareesuwan et al., 1996b). All artemisinin drugs prevent the development of ring stage parasites to the more mature pathogenic stages that rosette and cytoadhere in the capillaries (Watkins et al., 1993; Udomsangpetch et al., 1996).

Despite the limitations of many of the reported clinical studies, artemisinin derivatives consistently produce faster relief of clinical symptoms and clearance of parasites from the blood than other antimalarial drugs (Hien and White, 1993). In around 90% of the patients given these drugs, the fevers resolved and the parasitaemias cleared within 48 hours of treatment. It has been estimated that they reduce the parasite biomass by a factor of approximately $10^4$ for each 36-48 hour asexual cycle of the parasite and by a factor of $10^2$-$10^8$ over a 3-day course of treatment (White, 1997a). Despite their short elimination half lives, i.e. 1.6-2.6 hours, artemisinin drugs are effective when given daily.

The problem with the artemisinin drugs is that when they are used alone over short periods i.e. less than 5 days , clearance of parasitaemia from the blood is only temporary in up to 50% of patients. This high rate of recrudescence results from the rapid elimination of these drugs and the need for the any antimalarial drug to be present in the blood at effective concentrations during four asexual cycles (>6 days) to ensure elimination of the parasite
(White, 1997a). Higher efficacy can be obtained by 5- and especially 7-day regimens but this is associated with reduced compliance in out-patients.

Experience, mainly from China, Myanmar, Thailand and Viet Nam continues to indicate that these drugs are remarkably well tolerated in adults and children, no serious adverse effects having been reported following their clinical use (for details on toxicity issues see section 3.7). They are reliably effective against multidrug-resistant falciparum malaria when combined with mefloquine (Nosten et al., 1994) but monotherapy in 5-day regimens does not appear to achieve 90% cure rates in any area (McIntosh and Olliaro, 1998). In areas of mefloquine-resistance, the combination of artemisinin derivatives and mefloquine improves parasite clearance compared with either drug alone but there is little published data on combination therapy with drugs other than mefloquine. However, a fixed combination of artesunate with lumefantrine is in advanced stages of development by Novartis Pharma A.G.

Data are limited on the use of oral formulations of artemisinin drugs in Africa. Artesunate and artemether have been shown to clear parasitaemias more effectively than chloroquine and sulfadoxine/pyrimethamine in Nigeria and Tanzania (Ain et al., 1996a, b; Ezedinachi, 1996).

3.6.2 Treatment of severe malaria

In 1993, WHO recommended that the use of parenteral artemether or artesunate should be confined to areas where quinine resistance is demonstrable since the limited data available did not show a marked advantage of these drugs over quinine (WHO, 1994).

Since then there have been several studies comparing artemisinin derivatives with quinine in the management of severe malaria. Small sample sizes, different routes of administration and study design make comparisons between the studies difficult. WHO/TDR has, however, coordinated four large trials comparing artemether and quinine in The Gambia, Kenya, Malawi and Viet Nam as well as smaller studies in Africa and South-East Asia to address this problem. Meta-analysis of mortality in these trials indicated that a patient treated with artemether had at least an equal chance of survival as a patient treated with quinine (McIntosh and Olliaro, 1998b). Artemisinin drugs cleared parasites faster than quinine in patients with severe malaria but fever clearance was similar. Parenteral artemether and artesunate are, however, easier to use than quinine and do not induce hypoglycaemia. Two of these studies i.e. those in Gambian children and in Viet Namese adults, demonstrated a significantly longer coma recovery times in artemether treated patients than in chloroquine or quinine treated patients; the reasons for this are unknown (van Hensbroek et al., 1996; Hien et al., 1996).

There is a persistent neurological deficit following cerebral malaria in 3% of adults and 10% of children. Only the Gambian study assessed this phenomenon, the results of which showed that children treated with artemether had a slightly lower prevalence of
residual neurological sequelae after 6 months follow up than those treated with quinine (van Hensbroek et al., 1996).

There is some evidence that severe malaria may alter the kinetics of artemunate but further studies are required to confirm this observation and determine whether it has clinically relevant therapeutic consequences.

3.6.3 As an antigamete drug

Artemisinin and its derivatives have a significant effect on gametocytogenesis. Laboratory studies have shown that they prevent gametocyte development by their action on the ring- and early (stage I-III) gametocyte-stages (Kumar and Zheng, 1990; Mehra and Bhasin, 1993). These observations have been confirmed by field studies (Chen et al., 1994).

Between 1992-1995, an assessment of gametocytaemia in over 5 000 adults and children in Western Thailand near the border with Myanmar showed that treatment of uncomplicated falciparum malaria with either artemunate or artemether greatly reduced gametocytaemia (Price et al., 1996). Compared with mefloquine, the artemisinin derivatives reduced gametocyte rates by a factor of eight in primary infections and by a factor of 18.5 in recrudescent infections. The risk factors associated with the presence of gametocytes were anaemia or patent parasitaemia on presentation, prolonged history of illness, recrudescent infection, splenomegaly and subsequent drug failure.

These results suggest that artemisinin based drugs may reduce transmission and, consequently, the spread of resistant strains. Recent epidemiological data from the same area suggest that despite the presence of suitable vectors and adequate climatic conditions, there has been a decrease in the incidence of falciparum malaria, but not vivax malaria, following the introduction in 1991 of the artemunate-mefloquine combination. During the same period, the sensitivity of the parasite to mefloquine did not decline in spite of having markedly done so during the period 1986-1991 when mefloquine was used alone.

Further studies are required in other locations to confirm these observations. Experience with primaquine, currently the only operationally useful gametocytocidal drug, indicate that its impact is influenced by the extent of the coverage of drug administration, the level of transmission and the presence of asymptomatic gametocyte carriers.

3.7 Toxicity issues

Prospective clinical studies of over 10 000 patients and the use of artemisinin drugs in several million patients, including post marketing surveillance of over 4 600 patients in Thailand, has not shown any serious drug related adverse effects. The most common adverse effects reported following the use of artemisinin drugs are headache, nausea, abdominal pain, vomiting and occasional diarrhoea, symptoms that are associated with
malaria and which resolve with appropriate treatment. There is some evidence from uncontrolled trials of a temporary suppression of reticulocyte response without anaemia, and the induction of blackwater fever at the same frequency as quinine has been reported in the treatment of severe malaria. Post marketing surveillance in Thailand also detected two cases of bleeding disorders that may have been related to artesunate administration (Ministry of Public Health, Thailand, 1996).

However, animal studies have demonstrated limited symptomatic and pathological evidence of neurotoxicity following the parenteral administration of high doses of either artemether or arteether (Brewer et al., 1992, 1994a, b; Petras et al., 1997). Both drugs produced a unique pattern of selective neuronopathy in brain stem nuclei in rats, dogs and rhesus monkeys. The probable “No Observed Adverse Effect Level (NOEL)” of arteether and, possibly also, of artemether ranges from about 6.25 mg/kg/day in the dog to 100 mg/kg/day in the monkey. In contrast, there has not been any reproducible data demonstrating such neurotoxicity of artesunate or artelinic acid in the rat with intramuscular doses of respectively up to 175mg/kg/day and 420 mg/kg/day. Studies in other species with artesunate and artelinic acid have not been carried out.

Neuronal damage occurs as chromatolysis and necrosis of a few scattered neurons in certain nuclei of the brainstem and cerebellar roof. Damage elsewhere in the central nervous system has not been confirmed.

It has been concluded, therefore, that the risk of clinical neurotoxicity in humans given oral or rectal formulations of artemisinin drugs is likely to be low. However, the parenteral use of artemether or arteether may carry some risk, although the “NOELs” for both compounds administered by this route in animals suggests that the doses used to treat malaria in man would be non toxic.

In fact, there is no clinical evidence so far of serious neurotoxicity from the use of any artemisinin drug in man in prospective studies of over 10,000 patients. In addition, a recent retrospective study in Central Viet Nam, where there has been extensive use of artemisinin and its derivatives, has failed to detect any drug induced changes in the evoked auditory potentials of children and adults who had received courses of artemisinin over one year (Hien T.T. personal communication 1998). This study has been repeated in Thailand with 80 patients who had 2 or more treatment courses of artemisinin derivatives. In addition, a further 1100 cases in Thailand have had full neurological examinations following treatment. No specific pattern of neurological abnormalities was seen in these patients (Report of the TDR Informal Consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives, 20 July 1998, Geneva).

Whilst these results suggest that the risk of severe adverse reactions to the artemisinins appears low, they do indicate the need for continued vigilance and for post-marketing surveillance in all countries where artemisinin drugs are marketed and used.
3.8 Resistance

There have been no reports of clinical resistance to the artemisinin drugs. Clinical isolates and laboratory stains have been shown to vary in their sensitivities to these drugs but there is no evidence that this is related to clinical failure (Basco and Le Bras., 1993; Wongsrichanalai, et al., 1997). However, artemisinin-resistant strains of *P. falciparum* (Inselberg, 1985) and *P. yoelii* (Peters, et al., 1993) have been developed in the laboratory although the trait was unstable.

Laboratory studies have also shown that strains resistant to mefloquine appear to be less sensitive to artemisinin. This is probably related to the fact that these two drugs are synergistic (Chawira et al., 1987; Ekong and Warhurst, 1990). Field observations support these laboratory observations. For example, a high sensitivity to mefloquine, quinine and artesunate *in vitro* has been observed in isolates from the Yaha District of southern Thailand, an area where mefloquine provides high cure rates in the treatment of falciparum malaria. Whereas in Tak Province on the Myanmar border, the sensitivity to artesunate and mefloquine decreased between 1991-1994, a period when neither artemisinin nor any of its derivatives were available in Thailand (Wongsrichanalai, et al., 1998).

There have been reports of reduced susceptibility of falciparum infections to artemisinin in areas of Yunnan Province, China bordering with the Lao PDR and Myanmar where the infrastructure of the health services has decreased, self treatment has increased and large population migrations occur (WHO, 1997).

There is no doubt that resistance to artemisinin will arise but it is impossible to predict where and when. The increasing use of artemisinin and its derivatives, particularly with unsupervised and incomplete regimens, is likely to be a risk factor. This use is most intense in some countries of South-East Asia where there are generally low levels of population immunity, and population movements lead to temporary exposure to intense transmission. These factors have contributed previously to the emergence of resistance to other antimalarial drugs and may play the same role in the emergence of artemisinin resistance.

These observations emphasise the need to (i) establish systems to detect changes in parasite susceptibility to these drugs, (ii) monitor their therapeutic efficacy on a regular basis, and (iii) develop strategies that may prevent or delay the development of resistance.

3.9 Use of drug combinations

The rationale for combining drugs with independent modes of action to prevent the emergence of resistance was first developed in antibacterial and antimalarial chemotherapy and has since been adopted in cancer chemotherapy and, more recently, in the treatment of AIDS and leprosy.
The principle is that resistance arises from mutations and the chance that a mutant will emerge that is resistant to two or more drugs is the product of the individual per parasite mutation rates if the genetic mutations that confer resistance are not linked. For example, if 1 in $10^{10}$ parasites are resistant to drug A and 1 in $10^8$ are resistant to drug B, only 1 in $10^{18}$ will be simultaneously resistant to both drug A and B. As most patients at presentation have between $10^8$ and $10^{12}$ malaria parasites, only approximately 1 in 100 million treated patients would have surviving drug resistant parasites (White, 1998).

The development of resistance depends in part on the pharmacokinetic and pharmacodynamic characteristics of drugs. Antimalarial drugs with long terminal half lives are particularly vulnerable to the development of resistance because (i) there is an increased chance that a new and unrelated infection may be acquired whilst drug concentrations following treatment have fallen below those sufficient to prevent parasite multiplication and radically cure the new infection and (ii) if the original infection is not radically cured, surviving parasites will be subject to drug pressure as asexual cycles are exposed to decreasing blood concentrations (Watkins and Mosobo, 1993; White, 1997). There is good evidence that short half-life antimalarial drugs are less vulnerable to the development of resistance.

Artemisinin and its derivatives have short half-lives and are the most potent and rapidly acting antimalarial drugs known. They reduce the parasite biomass by around 10 000 fold for each asexual cycle and, at present, resistance to them has not been reported. Combinations of artesunate and mefloquine, and artemether with lumefantrine have both been shown to be highly active against multidrug resistance falciparum infections. There is evidence (see section 3.6.3 above) that the combination of artesunate and mefloquine may have played a role in both slowing down the development of resistance to mefloquine as well as reducing malaria transmission in an area of high mefloquine-resistance in Thailand (Price et al., 1997). This has been attributed to two factors: (i) the combination ensures high cure rates since the residuum of parasites remaining after the action of artesunate treatment for three days is exposed to maximum concentrations of the more slowly eliminated mefloquine. Only this residuum (maximum of $10^5$ parasites) is exposed to mefloquine alone so that the selective pressure for the emergence of mutants with reduced sensitivity to mefloquine is reduced considerably and (ii) artesunate reduces gametocytaemia rates and thereby transmission, so reducing the selection pressure for the spread of resistance.

Combinations of artemisinin derivatives could also have a potential role in Africa in slowing the development of resistance to other antimalarial drugs such as chloroquine and sulfadoxine/pyrimethamine.

Combining drugs may lead to altered pharmacokinetics, decreased efficacy and increased adverse reactions. However, there seem to be no drug interactions or increased adverse reactions to combining artemisinin derivatives with either mefloquine of lumefantrine but pharmacokinetic and tolerability as well as safety studies are needed for
other potential drug combinations (see section 4.2 below for list of potential drug combinations).

The use of combinations obviously increases the direct cost of treatment. For example, the addition of artesunate to mefloquine increases the cost by around 50%. If an adult dose of chloroquine or sulfadoxine/pyrimethamine costs US$ 0.10-0.20, the addition of artesunate would make the price US$ 1.80 – 2.20 (according to current prices of artesunate in China and Viet Nam), an increase of around 10-20 times. The cost of treating a 20 kg child would be about US$ 0.70 (White, 1998). These costs, however, should be offset against the potential indirect savings from both reduced morbidity and the costs of treating recrudescences (Bloland et al., 1993; Sudre et al., 1992).

Ideally, the components of combinations should be formulated into a single tablet or capsule but this would be considered as a new drug and require costly pharmacokinetic, toxicological studies for registration. A less satisfactory but simpler alternative would be to combine the separate components in blister packs as in multiple drug therapy of tuberculosis and leprosy. Licensing would be easier but the drugs in the combination would need regulatory approval. Dual prescription would be the cheapest approach but compliance would be a major problem.

3.10 Suppository formulations

The rectal administration of antimalarial drugs for severe malaria or patients to which oral treatment can not be given has several advantages. It is simple and can be done by unskilled persons. It avoids the problems of parenteral administration, including the use of non sterile or incorrect injections and the risk of transmitting other diseases such as hepatitis and HIV. Thus, it has the potential as an life-saving measure at the community level of health care where the administration of injectable administration may not be possible and high fatalities may be observed during transfer to the hospital.

Most of the experience with artemisinin suppositories comes from China and Viet Nam (Li, 1984; Li et al., 1985; Hien et al., 1991, 1992; Cao et al., 1997; Ha et al., 1997). These studies showed consistently that artemisinin suppositories were very well tolerated and rapidly cleared parasitaemia. The initial doses used varied between from 10-40 mg/kg but it remains to be determined whether the total dose and the administration schedule can be optimised further. There are few published reports on the pharmacokinetics of suppository formulations of artemisinin and its derivatives to optimise dosage schedules. Such reports show, however, that rectal administration leads to variable absorption of the drugs although the clinical efficacy of such suppositories in studies to date is comparable with that seen with oral or parenteral routes of administration. The only adverse effect reported was a transient depression of reticulocytes that did not translate into anaemia and returned to normal without treatment.
In initial trials in Thailand, 200mg artesunate rectocaps were given in the following regimens: 1600mg total dose over 3 days and 1200-1600mg total dose over 60 hours (Looareesuwan et al., 1995, 1997). More frequent administration in the first 24 hours resulted in faster parasite clearance but there was no difference in fever clearance times. In these trials and others in Myanmar, rectocaps were well tolerated and rapidly effective but it remains unclear whether the total dose and administration schedule can be optimized. Studies have also shown the efficacy and safety of the intrarectal administration of injectable artemether (Teja-Isavadharm et al., 1996).

Based on these experiences, WHO/TDR is developing, with industrial partners, gelatin-covered capsules of artemunate. The objective is to provide emergency treatment of patients at the periphery until oral drugs can be given or the patient can be referred to a facility where parenteral treatment is possible.

Artemisinin suppositories are marketed in Viet Nam. More recently dihydroartemisinin suppositories have been registered and marketed in China and artemunate rectocaps in Brazil, Côte d’Ivoire and Thailand.

4. PRIORITY AREAS FOR RESEARCH AND DEVELOPMENT

4.1 Basic research

- Studies on the mode of action and mechanism of resistance.
- Identification of genetic markers of resistance.
- Studies on the mechanism of selective toxicity.

4.2 Treatment of uncomplicated malaria

- Clinical evaluation of combinations of artemisinin derivatives with other antimalarial drugs, such as sulfadoxine/pyrimethamine, amodiaquine, chloroquine, pyronaridine, doxycycline and tetracycline to determine pharmacokinetic interactions, efficacy and tolerability and their impact on the development of resistance to the components. These studies, particularly with sulfadoxine/pyrimethamine, should be given the highest priority.
- Determination of the optimum regimens for the oral administration of dihydroartemisinin and artemether.
- Studies on the potential role of artemisinin derivatives in the treatment of chloroquine-resistant vivax malaria.
4.3 Compliance issues

- Studies to determine whether the regimens of artemisinin derivatives can be shortened, without loss of efficacy, when used in combination with other drugs.

- Studies on presentation and packaging of artemisinin-based drugs to improve compliance.

4.4 Treatment of severe malaria

- Determination of optimal regimens for parenteral and rectal administration of artemisinin derivatives.

- Determination of the speed and reliability of absorption of intramuscular and rectal administration of artemisinin derivatives.

- Determination of the clinical significance of delayed recovery from coma following administration of artemisinin derivatives.

4.5 Use in Pregnancy

- Determination of the safety of artemisinin drugs in the first trimester of pregnancy by follow up of patients inadvertently given drugs during the early stages of undisclosed pregnancies.

4.6 Anti-gametogenesis activity

- Determination of the importance of the activity of artemisinin drugs on gametocytogenesis in different epidemiological situations, with particular reference to malaria incidence and transmission.

4.7 Monitoring of adverse reactions

- Expansion of post marketing surveillance, currently only carried out in Thailand, to other countries where artemisinin and its derivatives are widely used.

- Continued surveillance of pregnant women given artemisinin drugs and all patients receiving repeated treatments, with special attention to the temporary suppression of reticulocyte response and neurotoxicity.

4.8 Monitoring of drug resistance and therapeutic efficacy

- Evaluation of recently developed protocols for monitoring therapeutic efficacy of antimalarial drugs for their applicability to artemisinin drugs.
• Further evaluation of *in vitro* tests for susceptibility of *P. falciparum* to artemisinin and its derivatives.

• Establishment of sentinel site monitoring of therapeutic efficacy testing.

4.9 **Antimalarial drug policy**

• Determination of the cost implications of the use artemisinin derivatives in combination with other appropriate drugs.

• Evaluation of the impact of global recommendations on the use of artemisinin and its derivatives on drug policies and their use in the public and private sector.

4.10 **Drug development and quality assurance**

• Development of improved formulations and new derivatives of artemisinin.

• Development of paediatric formulations for oral administration.

• Technology transfer to improve standards of manufacture of all formulations to GMP.

• Improvement of shelf life of formulations.

• Strengthening of national and regional regulations and capacities for quality assurance of artemisinin and its derivatives.

5. **RECOMMENDED REGIMENS**

5.1 **Treatment of uncomplicated malaria**

(i) **Combination therapy**

Artemisinin and its derivatives should be administered in combination with another effective blood schizontocide to reduce recrudescences and to slow the development of resistance. At present data only support the operational use of the combination with mefloquine (15-25 mg base/kg) but a fixed combination of artemether with lumefantrine is at an advanced state of development and research on other combinations is also being carried out. Administration of mefloquine on the second or third day considerably reduces the risk of vomiting once the clinical condition has been improved. Tolerance to the 25 mg base/kg doses of mefloquine may be further improved by administering 15 mg base/kg on the second or third day with the rest 6-24 hrs later. If compliance is a concern, mefloquine can be given
on the first day. The dose of mefloquine depends on the local sensitivity of the parasite to mefloquine.

The combination of dihydroartemisinin with mefloquine and other drugs is still being evaluated in clinical trials.

- **Artemisinin**: 20 mg/kg as a divided loading dose dose on the first day, followed by 10 mg/kg once a day for a further 2 days, plus mefloquine (15-25 mg base/kg) as a single or split dose on the second or third day.

- **Artesunate**: 4 mg/kg once a day for 3 days, plus mefloquine (15-25 mg base/kg) as a single or split dose on the second or third day.

- **Artemether**: 4 mg/kg once a day for 3 days, plus mefloquine (15-25 mg base/kg) as a single or split dose on the second or third day.

(ii) **Monotherapy**

In those situations where the use of artemisinin combinations is impossible, for example because of patient intolerance to mefloquine, monotherapy with artemisinin drugs may be used in regimens of 7 days with every effort being made to ensure compliance. Administration of shorter regimens to non-immune patients leads to unacceptably high levels of recrudescences.

- **Artemisinin**: 20 mg/kg in a divided loading dose on the first day, followed by 10 mg/kg once a day for 6 days.

- **Artesunate**: 4 mg/kg in a divided loading dose on the first day, followed by 2 mg/kg once a day for 6 days.

- **Artemether**: 4 mg/kg in a divided loading dose on the first day, followed by 2 mg/kg once a day for 6 days.

There are limited data on dihydroartemisinin and further research is required to determine optimal dosage regimens.

5.2 **Treatment of severe and complicated malaria**

The following schedules are recommended for adults and children over 6 months. However, more research is required to determine optimal regimens.
Intramuscular artemether

3.2 mg/kg as a loading dose on the first day, followed by 1.6 mg/kg daily for a minimum of 3 days until the patient can take oral therapy of an effective antimalarial. The daily dose of artemether can be given as one single injection. In children, the use of a 1ml tuberculin syringe is advisable since the injection volumes will be small. A formulation (40 mg/1ml) that is more easily used in children is available from one manufacturer.

Intravenous artesunate

2.4 mg/kg as a loading dose on the first day, followed by 1.2 mg/kg daily for a minimum of 3 days until the patient can take oral therapy of an effective antimalarial.

The anhydrous acid contents are dissolved in 0.6ml 5% (w/v) sodium hydrogen carbonate. The solution should be prepared just before use, because of the instability of the acid, and be diluted with 5.4 ml of 5% (w/v) dextrose solution or dextrose in normal saline.

6. USE IN PREGNANCY

When artemisinin drugs are given to laboratory animals, they can induce foetal resorption even at relatively low doses of 1/200 -1/400 of the LD$_{50}$ i.e. above 10 mg/kg (WHO, 1994). There is no evidence from preclinical studies that these drugs are mutagenic or teratogenic. Limited clinical experience to date, including a specific study of two hundred babies followed for two years after treatment of their mothers with artesunate during pregnancy, has not demonstrated any toxicity.

For the management of uncomplicated malaria in pregnancy, artemisinin and its derivatives can be used in the second and third trimester, but their use in the first trimester is not recommended.

In severe malaria, artemisinin derivatives are the drugs of choice in the second and third trimester. For the treatment of severe malaria in the first trimester, the advantages of artemisinin drugs over quinine, especially the lower risk of hypoglycaemia, must be weighed against the fact that there is still limited documentation on pregnancy outcomes following their use.

The inadequacy of current knowledge on the use of these drugs during pregnancy should be understood by care providers, and if possible, all pregnancies exposed to these drugs should be monitored. Reports of all clinical outcomes, both successful and adverse events should be made to regulatory authorities.
7. RECOMMENDATIONS AND CONCLUSIONS

Artemisinin and its derivatives are the most rapidly acting antimalarial drugs and are effective against falciparum malaria including multidrug resistant infections. They are, at present, the only group of antimalarial drugs to which resistance of \textit{P. falciparum} has not yet developed in the field. They have therefore an essential role to play in malaria control. This depends on ensuring that they are: (i) affordable to populations in need, (ii) of an acceptable quality, and (iii) used rationally and protected for as long as possible against the development of acquired drug resistance by the parasite. This will require not only further research but also the development, implementation and evaluation of global and national policies on their registration and use, and the cooperation of the public and private health sectors as well as the community at large.

7.1 Use

7.1.1 Artemisinin and its derivatives are safe and effective alternatives to quinine for the treatment of severe malaria. In areas where \textit{P. falciparum} sensitivity to quinine is reduced, artemisinin and its derivatives are the treatment of choice. In other areas, a change from quinine to artemisinin and its derivatives may not necessarily improve survival, yet these drugs may be preferred because of their fewer side-effects and ease of administration.

7.1.2 Artemisinin and its derivatives are potent and effective drugs for the treatment of uncomplicated malaria, but, at present, the use of these drugs should be limited to patients infected with multidrug-resistant malaria until the results of further research is available.

7.1.3 To improve efficacy and delay the onset of resistance, these drugs should always be used in combination with another effective antimalarial. Under exceptional circumstances, such as when there is a history of an adverse reaction to the combination agent, artemisinin monotherapy may be indicated, but a 7-day course of treatment is recommended and an effort should be made to ensure compliance.

7.1.4 In areas where mefloquine is already the first-line drug or a change to mefloquine is being considered, a 3-day course of an artemisinin drug should be given in combination with mefloquine.

7.1.5 Combination therapy with artemisinin and its derivatives could have the potential to slow the development of resistance to each component and is an attractive and promising strategy for the treatment of malaria in areas where chloroquine, amodiaquine, or sulfadoxine-pyrimethamine is the first-line drug, and where there is already evidence of chloroquine resistance. It is a matter of urgency that studies be conducted to evaluate the tolerability, efficacy, effectiveness, and cost of
various combination therapy strategies, particularly related their potential use in Africa south of the Sahara.

7.1.6 The use of parenteral preparation of the artemisinin drugs in patients who can take oral medications is not warranted.

7.1.7 This group of drugs is not indicated for the treatment of malaria due to Plasmodium malariae, P. ovale, or chloroquine-sensitive P. vivax. Research is needed into the use of these drugs for the possible treatment of chloroquine-resistant P. vivax.

7.1.8 Artemisinin and its derivatives should not be used for chemoprophylaxis.

7.2 Registration

7.2.1 Since artemisinin and its derivatives are among the most effective antimalarials known, it is important that their use is regulated. National governments should develop policies regarding their manufacturing, importation, promotion, distribution and use in order to prevent or delay the development of resistance. It is important to inform and elicit the support of all providers of care and those involved in distribution and selling of these drugs in the implementation of these policies. Supplies through aid agencies and community service organizations should also be in accordance with the national policy.

7.2.2 Many artemisinin group drugs are not produced to the internationally agreed standards of Good Manufacturing Practice (GMP). Drugs of uncertain quality and efficacy are in circulation. Very high priority should be placed on using GMP products. In situations where this is not possible, WHO will assist governments in selecting products for registration and help to assure quality, efficacy and safety through:

(a) the WHO Certification Scheme, which provides information on the regulatory status of a given product in the exporting country; and

(b) technical co-operation to national governments to develop systems for drug quality assessment/assurance.

7.2.3 In view of the lability of these drugs, special attention should be paid to planning of purchases, their sources, ordering, shipping, storage and distribution.
7.3 Monitoring of drug susceptibility and post-marketing surveillance

7.3.1 There is a serious concern that the widespread use and misuse of these drugs may encourage the development of parasite resistance. Monitoring of resistance is the responsibility of national malaria control programmes and should be conducted in sentinel sites on a regular and repetitive schedule. It is advisable that the response of patients to standard treatment should be followed in order to detect any change which might be a sign of decreasing drug susceptibility of the parasite.

7.3.2 Wherever these drugs are introduced, post-marketing surveillance should be established to identify problems related to quality, stability, efficacy and adverse reactions. Although there is now a greatly increased body of information confirming the safety of standard regimens with these drugs, it is still desirable that the long-term results of treatment be followed with regard to delayed toxicity, particularly among pregnant women and patients who have received repeated treatments.

7.4 Information

7.4.1 Clear guidelines on the use of artemisinin and its derivatives should be produced by national authorities and distributed to all providers of care and those involved in distribution and selling of drugs. This includes national drug formulary and pharmacy guidelines, as well as practical information on indications and dosage.

7.4.2 To avoid consumer misuse, it is important that drug dispensers and the general public as potential or actual patients be educated in the correct use of artemisinin and its derivatives, in particular the importance of compliance.

7.4.3 Donor agencies, Consumer Service Organizations (formally NGOs) and pharmaceutical companies should be discouraged from promoting or importing these drugs, except through official authorized channels.

7.4.4 Countries facing mutual problems of multidrug resistance and using artemisinin and its derivatives should develop intercountry mechanisms for exchanging information and experiences on drug policy and use, monitoring of drug efficacy and post marketing surveillance.
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