World Health Organization

WHO/CDS/MAL/2003.1094
WHO/RBM/TDR/Artemisinin/03.1

Assessment of the safety of artemisinin compounds in pregnancy

Report of two informal consultations convened by WHO in 2002 (Roll Back Malaria and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases)

Concept and design: Jocelyne Bruyère

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2003

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BACKGROUND AND EXECUTIVE SUMMARY

Various artemisinin compounds have been used as treatment for different forms of malaria since the early 1980s, initially in China, where they were first developed, and subsequently in many other countries. The literature on their use in pregnancy has been limited and animal studies have suggested that their use in pregnancy be restricted. With the increasing amount of interest in artemisinin combinations and artemisinin compounds in general, more studies – preclinical and clinical – are being envisaged and undertaken.

In 2001, a WHO report concluded:[1] "Preclinical studies have consistently shown that artemisinin and its derivatives do not exhibit mutagenic or teratogenic activity, but all of these drugs caused fetal resorption in rodents at relatively low doses of 1/200-1/400 of the LD50, i.e. > 10 mg/kg, when given after the sixth day of gestation. Reports on the use of these drugs during pregnancy are limited. However, malaria can be particularly hazardous during pregnancy. Artemisinin and its derivatives are therefore the drugs of choice for severe malaria and can be used for treatment of uncomplicated malaria during the second and third trimester of pregnancy in areas of multiple drug resistance. Owing to lack of data, their use in the first trimester is not recommended. The inadequacy of current knowledge on the use of these drugs during pregnancy should be understood by prescribers and all such use should, in principle, be monitored. Clinical outcomes of both a successful and adverse nature should be reported to regulatory authorities."

With more data becoming available it was time to re-evaluate existing data and policies on the use of artemisinin compounds in pregnancy. The 2000 WHO recommendations were reviewed in two consultations held in WHO in May and July of 2002. The meeting reports are attached herewith.

These reviews concluded with the following WHO recommendations for the use of artemisinin compounds in pregnancy.

WHO position statement on the current use of artemisinin derivatives in pregnancy

Infection with *Plasmodium falciparum* malaria in pregnancy is dangerous to both the mother and her child, so efficacious treatment is important. There are limited data on the clinical safety of antimalarial therapies in pregnancy. Artemisinin compounds, alone or in combination with other antimalarials, represent a relatively new and highly efficacious treatment for malaria, and it is important to determine their safety and efficacy in pregnancy.

Published data on 607 pregnancies in which artemisinin compounds were given during the 2nd or 3rd trimesters no evidence of treatment-related, adverse pregnancy outcomes. Similar data show normal outcomes in 124 pregnancies exposed to artemisinin compounds in the 1st trimester. These numbers are too small to provide an adequate profile of the safety of these compounds when used to treat malaria in pregnancy.

In animal studies with artemisinin compounds, there is clear evidence of death of embryos and some evidence for morphological abnormalities in early pregnancy. There is also some evidence for adverse effects on fetal body weight and survival when the drug is given later in pregnancy. Further work is required to better understand the relevance of the animal data for humans.

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[1] *Antimalarial drug combination therapy*. Report of a WHO Technical Consultation, Geneva, 4-5 April 2001 (document WHO/CDS/RBM/2001.35, available on request from CDS, World Health Organization, 1211 Geneva 27, Switzerland. Also available at: http://www.rbm.who.int/).

Presently, artemisinin compounds cannot be recommended for treatment of malaria in the 1st trimester. However, they should not be withheld if treatment is considered to be lifesaving for the mother and other antimalarials are considered to be unsuitable. Because the safety data are limited, artemisinin compounds should only be used in the 2nd and 3rd trimesters when other treatments are considered unsuitable.

There is a need for further evidence of the safety of artemisinin compounds in pregnancy. All pregnant women treated with artemisinin compounds should be carefully followed up to document the pregnancy outcomes and subsequent development of the child and reported to the appropriate authorities.

To guide the further development of policies on use of artemisinin derivatives, alone or in combination, during pregnancy, additional research and documentation of the efficacy and safety of the compounds as therapy for malaria, and as intermittent preventive treatment for malaria, is planned.

WHO is monitoring the accumulating evidence on safety and efficacy of artemisinin compounds used in pregnancy. This position statement is under continuous review and will be updated as needed.

REPRODUCTIVE RISK ASSESSMENT OF ANTIMALARIAL THERAPY WITH ARTEMISININ COMPOUNDS:

Report of an informal consultation convened by WHO, Geneva, 29–30 May 2002

Statement of issues

Various artemisinin derivatives have been prescribed as treatment for different forms of malaria since the early 1980s, initially in China, where they were first developed, and subsequently in many countries in Asia, Europe, North and South America and Africa.

The compounds of greatest therapeutic interest at present are the closely related dihydroartemisinin, artesunate, arteether and artemether. For many purposes, these are co-formulated or co-prescribed with other antimalarial drugs, such as lumefantrine and chloroquine. Sole use of an artemisinin derivative is not recommended except for the short-term emergency use of rectal artesunate to treat patients with severe falciparum malaria before they can receive conventional parenteral therapy.

The artemisinin compounds have been formulated as oral preparations, intravenous and intramuscular injections, and rectal suppositories.

Past and ongoing formal clinical studies in several thousand patients have demonstrated the general safety and efficacy of artemisinin derivatives in adults and young children, principally in falciparum malaria, and their desirable clinical properties, such as rapidity of action and maintained activity even in patients carrying multidrug resistant parasites.

Formal non-clinical testing of one or other of the compounds, either on its own or co-formulated with another antimalarial drug, has been undertaken by WHO and independently by a number of pharmaceutical companies. Each developer has made a full regulatory submission of their own pharmaceutical, non-clinical and clinical data to major Western, Asian and African regulatory agencies, and formal approval has been obtained for many of them as prescription medicines and as oral or rectal medicines suitable for community use in countries with less developed medical services.

The regulatory approvals in Western countries have been couched in conventional terms to cover use of the medicines in adult men and in women of child-bearing potential provided they are not pregnant, reflecting the limited clinical information about safety in pregnant women. Their use in pregnancy has been left for decision by the physician making a risk-benefit assessment in the individual patient. There is evidence from community use in several countries of the lack of harm to the mother and fetus. This evidence has not yet been presented for formal regulatory assessment.

Additionally, recommendations for use in young children and in mothers during breast-feeding have been very restrictive or tentative, mainly due to lack of regulatory submission of clinical evidence of safety. Again, there is field experience and some published information about their safety in these phases of the human reproductive cycle.

Until very recently, results from a variety of studies of all phases of non-clinical reproduction toxicity tests were interpreted as indicating that, although all the artemisinin derivatives could be shown to be embryotoxic after certain high doses in conventional tests of reproductive toxicity in the rat and rabbit, they did not affect the fertility or postnatal development and maturation of offspring of dosed dams. New results however, from studies of a new combination of artesunate with chlorproguanil and dapsone, have suggested a possible divergent pattern of effects on development of the fetus.

The purpose of this Informal Consultation was to enable a group of scientific and clinical experts to review all the clinical evidence in humans and the non-clinical experimental results about reproduction toxicity testing and to consider their significance for clinical use of artemisinin compounds in women who might be pregnant or lactating, and in young children.

Information available

Prior to the meeting, full reports of the non-clinical reproduction toxicity testing of dihydroartemisin, artesunate, arteether and artemether, alone or in combination with other antimalarial drugs, were made available to the experts. These were reports that had already been accepted and evaluated by regulatory agencies or were about to be submitted for official approval, and so they comprised the complete set of available data as far as known to WHO and the manufacturers, who generously permitted use of their proprietary information.

The reports were of studies of fertility and early fetal development, maternal and fetal toxicity, teratogenicity, peri– and postnatal dosing and subsequent development of pups. All had conformed to good laboratory practice (GLP) and the experiments had been conducted according to the comprehensive requirements of major regulatory agencies.

It was noted that the considerable difficulty of analysing the drugs in biological matrices had so far made it impossible to provide information about the kinetics and metabolism of the compounds in pregnant animals, or about transfer of the drug and metabolites across the placenta or into the milk. It was also noted that, while the antimalarial mechanism of action of the artemisinin compounds is not yet certain, it probably involves initial conversion of all derivatives to dihydroartemisinin as a major active metabolite.

The lack of data was not, however, felt to prevent proper assessment of available experimental information but only to limit the ability to come to unqualified conclusions.

Presentations and discussions

After an opening statement on the purpose of the meeting by Dr Gomes, Dr Nahlen described the general nature of malaria and the problems of its treatment in African countries, and Dr McGready discussed similar aspects of malaria in SE Asia including accounts of several formal clinical trials and community surveillance schemes which she and her colleagues had undertaken.

The experts then met in closed session to review all the detailed non-clinical experimental data they had examined, to link those findings to general experience of the artemisinin compounds in laboratory and field use, and to evaluate all the information to arrive at a unanimously agreed set of conclusions (see below). The significance of the present reproduction toxicity testing results for clinical use of artemisinin compounds in potentially pregnant women and in young children was evaluated, as were the most immediately valuable additional clinical and laboratory studies.

The provisional conclusions were discussed in open session with members of the WHO secretariat to ensure they covered the necessary topics. Prior to their finalization and presentation here, the conclusions were also reviewed by all the experts.

Conclusions

1. Evaluation of experimental results

The following points refer to all the artemisinin analogues, listed in Appendix I, for which data were available to the experts.

1.1 It was agreed that artesunate and all the other artemisinin analogues are developmental toxicants in the rat and rabbit. The dose-response relationships for the compounds are unusually steep. The effects are dominated by embryo-lethality and late resorptions and a few instances of morphological abnormalities, all under circumstances not related to maternal toxicity.

1.2 All the artemisinin analogues have been associated with embryo-lethality over a narrow dose range. General experience has shown that morphological abnormalities and embryo-lethality are part of a continuous spectrum. A small change in dose or other factors may favour the occurrence of one over the other.

1.3 There have been minor indications in some experiments of pre-implantation loss and possibly of some change in sperm counts, but neither has been systematically studied.

1.4 Fertility has not been affected.

1.5 The main effect of embryo-lethality, as seen in many embryo toxicity studies, is not necessarily predictive of the same effect in humans. If there were a similar action in pregnant women it might become apparent during the first trimester of pregnancy.

1.6 The mechanism of the developmental toxicity in animals is not known. It is not clear whether the initial site of action is in the mother, the fetus, or the placenta. In addition to the predominant embryo-lethality, there are instances of effects on development of the cardiovascular system, the axial skeleton, and the limbs, but these do not suggest the nature of the toxic action.

1.7 There is decreased sensitivity to the effect on fetal growth or survival following dosing in later stages of pregnancy. Maternal dosing during lactation, post-natal development and maturation has not led to any convincing toxic effects.

1.8 The limited experimental results available about various combination therapies of artemisinin analogues and other antimalarial drugs (chlorproguanil and dapsone) do not show increased toxicity in comparison with the artemisinin compounds alone.

1.9 Doses in animals associated with effects on the embryo are similar to those used in clinical practice, but as there are no relevant pharmacokinetic data it is impossible to interpret this information in terms of systemic exposure, or to estimate a safety margin in a conventional manner.

2. Clinical implications

2.1 It is not possible to predict from the animal findings the exact nature of the harmful effects that might be produced in women. However, the predominant experimental findings do suggest that if there were similar clinical effects, they would be likely to become apparent during the first trimester of pregnancy, e.g. as early loss of pregnancy or difficulty in becoming pregnant.

2.2 The clinical information is encouraging in not showing any evidence of harm to mothers or fetuses at any stage of pregnancy.

The number of women and their babies formally studied after dosing during the first trimester of pregnancy being small (44 in SE Asia, 80 in Africa), any conclusion about safety can only be of limited power. No study has been specifically designed to examine early pregnancy loss.

A much larger number of women has been followed after treatment during the second and third trimesters (417 in SE Asia, 207 in Africa) and there is greater confidence in the safety of treatment during that period, based on clinical findings and the results of animal experimentation.

2.3 Studies of babies born to mothers dosed during pregnancy or lactation have not shown evidence of physical or neurological abnormalities during development, and this is supported by the results of appropriate animal experiments.

2.4 Since brain development in man continues throughout pregnancy and the first two years of life, it is relevant that no developmental or neurological abnormality has been detected in formal surveillance of large numbers of infants treated with artemisinin compounds from three months of age onwards.

3. Considerations related to risk

3.1 It is important that pregnant women with malaria are treated because of the serious adverse effects of the disease on the mother and fetus, and the public health risk of continuing gametocyte transmission in the community.

There is clear evidence of benefits to the mother and fetus of treating pregnant women who have falciparum malaria with artemisinin compounds.

3.2 Having reviewed all the experimental evidence on the developmental toxicity of artemisinin compounds, the experts considered it reasonable that these drugs should continue to be available for the treatment of women with malaria, irrespective of their pregnancy status.

3.3 It is very important that further clinical and experimental work be carried out to clarify the extent and nature of adverse developmental actions of these drugs.

It was recommended that a clinical monitoring programme be established to assess the outcome of pregnancy in women treated with any antimalarial drugs, as the formal evidence about safety during pregnancy for any of them is weak.

4. Limits to conclusions

4.1 The lack of pharmacokinetic information made it impossible to compare therapeutically and toxicologically relevant exposures in women and animals.

4.2 The experimental data available did not permit the experts to compare the relative developmental toxicities of the different artemisinin analogues.

4.3 There were too few data to support a proper comparison of the developmental toxicity of combinations of artemisinin analogues with different antimalarial drugs.

4.4 The experts did not have the information to compare artemisinin compounds with other classes of antimalarial drug in regard to their safety for use in pregnancy.

5. Research needs

5.1 It would be particularly valuable to repeat the embryotoxicity experiments in the rat and rabbit in such a way that pharmacokinetic information is obtained about the exposure of dams and fetuses. More detailed study of the nature of the toxic effect on embryos is required, and would likely provide clues as to the site and mechanism of toxicity, which would be of value in extrapolating the results to humans. Any action on the hormonal status of dams could be further explored, as could any direct action on the fetus, e.g. through in vitro experiments using embryo culture.

5.2 For each artemisinin analogue, it is very important to compare pharmacokinetic findings in animals with those in pregnant women to gain better understanding of its margin of safety. Understanding the mechanism of toxicity would greatly increase the value of advice about safe use of these drugs in pregnancy, especially in the first trimester.

5.3 Monitoring should be implemented to follow the outcomes of pregnancies of women exposed to artemisinin compounds at any stage of pregnancy, especially in the first trimester. Strategies should be devised to monitor early pregnancy loss, e.g. time-to-pregnancy studies associated with exposure to artemisinin compounds.

Experts and authors of the preclinical meeting report

Dayan, A. 21 Heathgate, London NW11 7AP, UK.
Tel./Fax: (+44) 208621 3528, e-mail: a.dayan@toxic.u-net.com

Brown, N. St George's Hospital Medical School, Department Anatomy and Developmental Biology, Cranmer Terrace, London SW17 ORE, UK.
Tel.: (+44) 208725 2830, Fax: (+44) 208725 0749, e-mail: nbrown@sghms.ac.uk

Faustman, E. Institute for Risk Analysis and Risk Communication, Department of Environmental Health, 4225 Roosevelt Way NE, Suite #100, Box 354695, Seattle, WA 98105-6099, USA.
Tel.: (+1) 206 685 2269, Fax: (+1) 206 685 4696, e-mail: faustman@u.washington.edu

McGready, R. Shoklo Malaria Research Unit, P.O. Box 46, Mae Sot 63110, Thailand.
Tel.: (+66) 55 531 531, Fax: (+66) 55 535 440, e-mail: shoklo@cscoms.com

Paulus, G. Leopold De Waelplaats 28/23, B-2000 Antwerp, Belgium.
Tel.: (+32) 3 238 7185, e-mail: guy@paulus.telenet.be

Piersma, AH. Laboratory for Health Effects Research RIVM, Antonie van Leeuwenhoeklaan 9, P.O. Box 1, 3720 BA Bilthoven, The Netherlands.
Tel.: (+31) 30 274 2526, Fax: (+31) 30 274 4446, e-mail: ah.piersma@rivm.nl

Sullivan, F. Harrington House, 8 Harrington Road, Brighton BN1 6RE, UK.
Tel.: (+44) 1273 55 3845, Fax: (+44) 1273 50 0723, e-mail: fsullivan@mistral.co.uk

WHO Secretariat

A. Bosman	RBM	e-mail: bosmana@who.int
M. Couper	EDM	e-mail: couperm@who.int
M. Gomes	TDR	e-mail: gomesm@who.int
K. Mendis	RBM	e-mail: mendisk@who.int
B. Nahlen	RBM	e-mail: nahlenb@who.int
P. Olliaro	TDR	e-mail: olliarop@who.int
P. Olumese	RBM	e-mail: olumesep@who.int
R. Ridley	TDR	e-mail: ridleyr@who.int

APPENDIX I: List of reports, publications, and other materials reviewed

Arteether

1. Project 392962: Study of fertility and early embryonic development to implantation with ACF ARE841 (arteether) in the rat (intramuscular injection) (1995).
2. Project 392951: Study for effects on pre- and postnatal development including maternal function with ACF ARE841 (arteether) in the rat (intramuscular injection) (1996).
3. Project 384197: First dose range-finding embryotoxicity study (including teratogenicity) with ACF ARE841 (arteether) in the rabbit (1996).
4. Project 605845: Supplementary study to the study of fertility and early embryonic development to implantation with ACF ARE841 (arteether) in the rat (intramuscular injection) (1996).

Artesunate

5. Report 1552/93-D6154: Artesunate: oral (gavage) study of embryo-foetal development in the rat (2002).
6. Report 1552/94-D6154: Artesunate: oral (gavage) study of embryo-foetal development in the rabbit (2002).
7. Artesunate for injection: embryotoxicity in rats (1985).
8. Artesunate for injection: toxicity studies on male reproductive system in rats (1985).
9. BDC003: Oral (gavage) rat developmental toxicity and littering dose-ranging study (1999).
10. BDC008: Oral (gavage) rat developmental toxicity rangefinding study (2000).
11. BDC009: Oral (gavage) rat developmental toxicity (and littering) study (2000).
12. BDC004: Oral (gavage) rat developmental toxicity and littering study (2000).
13. BDC007: Oral (gavage) rat developmental toxicity and littering dose ranging study (2000).
14. BDC005: Oral (gavage) rabbit developmental toxicity dose ranging study (1999).
15. BDC006: Oral (gavage) rabbit developmental toxicity study (2000).
16. Oral (gavage) study of embryo-foetal development in the rat (2000).

Dihydroartemisinin

17. Report 158884: Embryotoxicity and teratogenicity study with ACF ARD842 (dihydroartemisinin) administered by oral gavage in wistar rats (1996).
18. Report 175218: Assessment of fertility and early embryonic toxicity of ACF ARD842 (dihydroartemisinin) administered by oral gavage in wistar rats (1997).
19. Report 175229: Assessment of prenatal and postnatal developmental toxicity and maternal toxicity of ACF ARD842 (dihydroartemisinin) administered by oral gavage in wistar rats (1996).
20. Report 139758: Embryotoxicity and teratogenicity study with report 158884: embryotoxicity and teratogenicity study with ACF ARD842 (1996) (dihydroartemisinin) administered by oral gavage in wistar rats (1996).
21. Report 139769: Embryotoxicity and teratogenicity study with ARD842 (dihydroartemisinin) administered by oral gavage in albino rabbits (1996).

Artemether

22. CGP 56696: An oral study for effects on embryo and fetal development in rats (1996).
23. CGP 56 696: An oral dose-rangefinding study for effects on embryo and fetal development in rabbits (1995).
24. CGP 56696: An oral study for effects on embryo and fetal development in rabbits (1996).

Chlorproguanil/dapsone/artesunate

25. Report 1552/45-D6154: (draft) Oral (gavage) study of embryo-foetal development in the rabbit (2001).
26. Oral (gavage) study of embryo-foetal development in the rat (2001).

Artemether/lumefantrine

27. CGP 56697: An oral embryo and fetal development study in rats (1995).
28. CGP 56 697: A follow-up dose- range-finding study for effects on embryo and fetal development in rats (1995).
29. CGP 56 697: An oral study for effects on pre- and postnatal development in rats (1996).

Chlorproguanil/dapsone

30. Report 1552/49: Oral (gavage) study of embryo-foetal development in the rabbit (2001).

Chlorproguanil/dapsone and chlorcycloguanil

31. Report 1552/38: Oral (gavage) study of fertility and embryo-foetal development in the rat (2001).

Clinical data

McGready R. et al. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1998, 92: 430-433.

McGready R. et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, 94:689-693.

McGready R. et al. Randomized comparison of quinine-clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 2001, 95:651-656*.

McGready R. et al. Artemisinin antimalarials in pregnancy: A prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. *Clinical Infectious Diseases*, 2001, 33:2009-2016.

McGready R., Nosten F. The Thai-Burmese border: drug studies of *Plasmodium falciparum* in pregnancy. *Annals of Tropical Medicine and Parasitology*, 1999, 93: Supplement No 1, S19-S23.

THE SAFETY AND EFFICACY OF ANTIMALARIAL THERAPY WITH ARTEMISININ COMPOUNDS IN PREGNANCY:

Report of an informal consultation of clinical investigators convened by WHO, Geneva, 22–23 July 2002

Background

Malaria in pregnancy poses serious risks for the mother and her infant. In areas of low malaria transmission, acute malaria causes abortions and stillbirths and mothers may die from the acute effects of the infection. In areas of high transmission, malaria can cause severe anaemia during pregnancy and, because of heavy sequestration of parasites in the placenta, low birth weight. Because low birth weight is such an important determinant of child survival, malaria in pregnancy is likely to result in an increase in infant mortality. For these reasons, protection of pregnant women against malaria is an important public health priority and a major objective of the Roll Back Malaria partnership. All pregnant women with documented or suspected malaria must be treated as soon as possible with a safe and effective drug. In some areas, antimalarials given as intermittent preventive treatment (IPT) are used to prevent malaria in pregnancy. Unfortunately there is little information on the safety of the antimalarials that are currently used to treat or prevent malaria in pregnancy, even though they were introduced into clinical practice many years ago. Furthermore, the efficacy of many of these drugs, such as chloroquine and sulphadoxine/pyrimethamine (SP), is now challenged by the spread of resistant parasites. There is, therefore, a need for careful evaluation of alternative, effective drugs, including artemisinin compounds, that can be used in the treatment and prevention of malaria in pregnancy. Artemisinin compounds, which have been shown to be safe and efficacious in children and non-pregnant adults, are already used widely in Asia and their use in Africa is likely to increase substantially in the next few years as drug policies change to meet the challenge of multidrug resistance.

Introduction

Concerns have been raised about the safety of artemisinin compounds in pregnancy following the detection in rats and rabbits of embryotoxicity and growth defects, including unusual limb in some studies, when pregnant animals were exposed to this group of drugs. After the meeting of experienced toxicologists was convened at WHO Geneva, 29-30 May 2002, to review in detail the data from all available preclinical studies (page 4 of this document), a further informal consultation of clinical investigators was held at WHO Geneva, 22-23 July 2002, to consider the safety of exposure to artemisinin compounds in pregnancy and make recommendations on their use in pregnant women. The specific tasks of the group were to:

- Review and discuss the report of the toxicologists referred to above and a further report produced by WHO on the pharmaco-vigilance of artemisinin-based combination therapies.
- Review a draft WHO position statement on the use of artemisinin compounds in pregnancy.
- Identify knowledge gaps on the safety and efficacy of artemisinin compounds in pregnancy.
- Identify priority areas for further research on the use of artemisinin compounds in pregnancy.

Review of the report on the reproductive risk assessment of artemisinin compounds

The group reviewed the toxicologists report in detail and considered its implications. Attention was focused primarily on infections caused by *Plasmodium falciparum*.

Points that were highlighted were:

- There are drugs that are in use in pregnancy, including antimalarials, that are embryotoxic and/or teratogenic in animals under certain conditions. However, the limb abnormalities seen in some studies with artemisinin compounds are unusual, and they occur at dosing levels similar to those used in man.
- Findings in animals may not be applicable to humans because the physiological factors that control pregnancy in rats and women, e.g. the balance between reproductive hormones, are very different. However, the relevance of the findings in animals to humans cannot, at present, be discounted.
- The risk of teratogenesis as a consequence of exposure to a high concentration of drug over a short period is likely to be higher in experiments in rats, in which critical developmental processes take place during just a few days, than in humans, in whom critical phases of development take place over a longer period of time.
- There are some reassuring, although limited, data on the safety of artemisinin compounds when given to pregnant women in each trimester. However, only about 100 women have been observed after exposure during the first trimester.
- There are other examples of situations in which preclinical data of concern have come to light after a drug has been used extensively in clinical practice without any reports of serious adverse events. In these circumstances, the usual course of action followed has been to undertake further preclinical studies and to reassess the risk- benefit relationship of the drug in question without necessarily recommending its withdrawal.

Review of the paper on pharmaco-vigilance

The group reviewed the paper produced by WHO on the pharmaco-vigilance of artemisinin-based chemotherapies in Africa, and heard an updated presentation on plans for work in this area. The proposal to establish pregnancy registers was of particular interest to the group. This will involve establishing prospective, active surveillance in sites where artemisinin-based combination therapy (ACT) is being used or will be introduced shortly.

The group noted that:

- Long-term follow-up of both the mother and her baby will be required. This will be achieved most easily in areas with an established demographic surveillance system.
- Documentation of all drugs taken during pregnancy will be difficult in areas where antimalarials and other drugs are available freely.
- Information on the safety of artemisinin compounds in the first trimester of pregnancy is likely to be obtained mainly as a result of inadvertent exposure of women to the drug in areas where artemisinin compounds are being used widely, rather than a result of intentional treatment.
- Establishing a reliable reporting system will require substantial investment and training. The pharmaceutical industry may be able to help with this in some circumstances.
- Surveillance at different sites will benefit from the use of common reporting forms for adverse events.
- Data from each site where surveillance is established should, whenever possible, be entered into a common database.

Discussions were held as to the size of the database needed to establish, with an appropriate degree of confidence, that a particular drug or drug combination is safe in pregnancy (it is never possible to establish this with complete certainty). Five thousand women was suggested as a reasonable target although it was pointed out that detection of a doubling in the rate of an individual malformation with an incidence of 1:1000, a representative rate for specific abnormalities, would require a much larger sample size than this.

Research needs

A number of research needs were identified.

In the preclinical area, more information is needed on:

- The relationship between the occurrence of embryotoxicity in animals and blood levels of artemisinin and its active metabolites.
- The mechanism by which adverse pregnancy effects in animals are brought about.
- Whether there are differences in the relative toxicities of different artemisinin compounds and ACT combinations.

Research priorities identified in the clinical area were:

- Collection of data on the safety and efficacy of different artemisinin compounds and ACT therapies in pregnancy, given in carefully controlled clinical settings and with effective clinical monitoring of outcomes, for treatment of symptomatic infection and for prevention of malaria during pregnancy.
- The risk-benefit ratio of adding artemisinin compounds to the currently recommended drugs for prevention of malaria in pregnancy.
- Study of the effects of HIV and administration of other drugs on the safety and efficacy of artemisinin compounds given during pregnancy.
- Studies on the pharmacokinetics of artemisinin compounds and ACTs in pregnancy under controlled clinical settings.

The group considered that determining the possible effect of widespread use of artemisinin compounds on early pregnancy loss would be extremely difficult. It was pointed out that there is little information on the use of artemisinin compounds during lactation but it was considered that this is unlikely to be a major concern as there is good evidence for the safety of artemisinin compounds in infants.

The group was asked to limit its considerations to the use of artemisinin compounds in pregnancy but members of the group stressed that there are few data on the safety of other antimalarial drugs, such as amodiaquine and S/P, that are currently being used to treat malaria in pregnancy. They recommended that this lack of information should be addressed through a comprehensive assessment of existing preclinical and clinical data as well as through prospective studies.

Draft statement

The group discussed in detail the draft WHO statement on the use of artemisinin compounds in pregnancy prepared by the secretariat, and modified it in light of the discussions held during the meeting. A consensus was achieved. It was agreed that the statement should be used as an executive summary for the report of the informal consultation and that both would be circulated widely to all relevant authorities.

The agreed statement has been placed as the summary of this document.

List of participants

Dayan A. 21 Heathgate, London NW11 7AP, UK.
Tel./Fax: (+44) 208621 3528, e-mail: a.dayan@toxic.u-net.com

Sullivan, F. Harrington House, 8 Harrington Road, Brighton BN1 6RE, UK.
Tel.: (+44) 1273 50 0723, Fax: (+44) 1273 55 3845, e-mail: fsullivan@mistral.co.uk

Greenwood, B. London School of Hygiene and Tropical Medicine, 50 Bedford Square, London, WC1B 3DP, UK.
Tel.: (+44) 207299 4707, Fax: (+44) 207299 4720, e-mail: Greenwood@lshtm.ac.uk

Nosten, F. Shoklo Malaria Research Unit, P.O. Box 46, Mae Sot 63110, Thailand.
Tel.: (+66) 55 531 531, Fax: (+66) 55 535 440, e.mail: shoklo@cscoms.com

Menendez, C. International Health Center, Hospital Clinic/University of Barcelona, Spain and Manhiça Health Research Centre, Manhiça, Mozambique.
Tel.: (+258) 1 810 002, Fax: (+258) 1 810 181, e-mail: cmenende@medicina.ub.es

Diap, G. Médecins Sans Frontières, Access to Essential Medicine, 8 Rue Saint Sabin, 75011, Paris, France.
Tel.: (+33) 1 4021 2929, Fax: (+33) 1 4806 6868, e-mail: Graciela_DIAP@msf.org

Steketee, R. Division of Parasitic Diseases, Centre for Disease Control and Prevention (CDC), Building 102, Room 1320, Mailstop F-22, 4770 Buford Highway, Atlanta, GA 30341-3724, USA.
Tel.: (+1) 770 488 7760, Fax: (+1) 770 488 7761, e-mail: ris1@cdc.gov

Mutabingwa, T. London School of Hygiene and Tropical Medicine-Gates Malaria Partnership, C/o Muheza Designated District Hospital, Private Bag Muheza, Tanzania.
Tel.: (+255) 27 264 1420, Fax: (+255) 27 264 4121, e-mail: tkmuta@ud.co.tz

Chintu, C. School of Medicine, University of Zambia, Box 50110, Lusaka, Zambia.
Tel.: (+260) 1 254 681, Fax: (+260) 1 254 681, e-mail: cchintu@zamnet.zm

Winstanley, P. Department of Pharmacology and Therapeutics, University of Liverpool L69 3GE, UK.
Tel.: (+44) 1517 94 5544, Fax: (+44) 1517 94 5540, e-mail: peterwin@liverpool.ac.uk

Kazembe, P. Ministry of Health, Paediatric Unit, Malawi.
Tel.: (+265) 721 555, Fax: (+265) 721 018, e-mail: pnkazembe@malawi.net

WHO Secretariat

D. Alnwick	RBM	e-mail: alnwick@who.int
A. Bosman	RBM	e-mail: bosmana@who.int
M. Couper	EDM	e-mail: couperm@who.int
M. Gomes	TDR/IDE	e-mail: gomesm@who.int
T. Kanyok	TDR/PRD	e-mail: kanyokt@who.int
K. Mendis	RBM	e-mail: mendisk@who.int
C.M. Morel	TDR	e-mail: morelm@who.int
B. Nahlen	RBM	e-mail: nahlenb@who.int
P. Olliaro	TDR/IDE	e-mail: olliarop@who.int
P. Olumese	RBM	e-mail: olumesep@who.int
R. Ridley	TDR/PRD	e-mail: ridleyr@who.int
M. Robalo	AFRO	e-mail: robalom@whoafr.org