

# Are artemisinin derivatives safe in neonates?

Primary Reviewer: **Malcolm Battin**<sup>1</sup>    Secondary Reviewer: **Nick White**<sup>2</sup>

First published online: 31<sup>st</sup> March 2006

<sup>1</sup> National Women's Hospital and Dept of Paediatrics, University of Auckland, New Zealand  
<sup>2</sup> Director, Wellcome Trust South East Asia Unit, Thailand

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

[http://www.who.int/child-adolescent-health/publications/CHILD\\_HEALTH/PB.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm)

**This review addresses the question:** *Are artemisinin derivatives safe in neonates?*

The WHO Pocketbook of Hospital Care for Children recommends quinine or artemisinin derivatives (artemether or artesunate) for the treatment of severe malaria. Quinine is recommended for most countries, except those in Southeast Asia and the Amazon basin. Whatever first-line therapy is used WHO now strongly recommends combination therapy; using an additional drug to which there is no resistance (suplethoxine-pyrimethamine, artemisinin-based combination therapy or clindamycin in combination with quinine). (Pocketbook chapter 6.2.1, page 141).

## INTRODUCTION

Malaria is a major health problem in the tropics, with 300–500 million new clinical cases annually [1]. The problem of drug resistance has driven research into, and use of, new agents. Artemisinin is the active ingredient in a Chinese herbal tea that has been used for 150 years to treat malaria. Artemisinin derivatives include artemether, artesunate, arteether and arteminate. These compounds are rapidly converted to the active metabolite dihydroartemisinin and act quickly against the parasite at a number of levels. Artemisinin and its derivatives inhibit an essential calcium adenosine triphosphatase, PfATPase 6 [2].

Artemisinin and its derivatives are an alternative to quinine in children and adults, particularly in areas of multi-drug resistance. They are considered safe and effective for treatment of uncomplicated malaria in adults and children [3] and recent randomised trials comparing artesunate and quinine from East Asia show clear evidence of benefit with artesunate [4]. In the largest multi-centre trial, which enrolled 1461 patients (including 202 children <15 y), mortality was reduced by 34.7% compared to the quinine group. The results of this and smaller trials are consistent and suggest that artesunate is the treatment of choice for adults with severe malaria. However, there is still insufficient data to make the same conclusion for children, particularly from high transmission settings; an individual patient data meta-analysis of trials comparing artemether and quinine showed no difference in mortality in African children.

Serious adverse neurological and cardiovascular effects are reported from animal studies using high dose arteether and artemether [5]. However, these effects are not reported from experience of clinical use in humans. Limited data are available from use in pregnancy including 607 pregnancies exposed in the second or third trimester and 124 pregnancies exposed during the first trimester. In all cases there was no evidence of adverse outcome but the numbers are considered too small to provide an adequate profile of safety [6]. In view of the limited safety data Artemisinin derivatives should be avoided in first trimester patients with uncomplicated malaria until more information is available.

Artemisinin compounds used either alone or in combination with other antimalarials are becoming common treatments and it is important to determine the safety profile in all age groups. This review intends to answer the question: Are artemisinin derivatives safe in neonates?

## METHODOLOGY

The search strategy chosen was that of Haynes et al "Clinical queries" in Pubmed. Utilizing Search By Clinical Study Category identifying therapy and using narrow search option was as follows: (Artemisinin OR artemether OR arteether OR artesunate OR artelinic acid OR dihydroartemisinin) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])). Similarly using the Find Systemic Reviews the search was (Artemisinin OR artemether OR arteether OR artesunate OR artelinic acid OR dihydroartemisinin) AND systematic[sb].

All identified abstracts were read, if there was any doubt as to the relevance of the article, the complete article was sourced. Articles were excluded if the study group did not include infants in first month of life or if the methods did not comply with the pre established criteria.

## RESULTS

Of the 239 RCT's identified six of these remained [7][8][9][10][11][12] when the search was limited to age group Newborn: birth to one month. To ensure no neonatal safety data was missed from studies classified as being performed in young infants the above search was also performed limited to Infant: birth to 23 months. 50 studies were identified but on reading the abstract all but 11 were excluded as being in the wrong age group. The complete article for these 11 studies was then sourced and read to identify the age of the study group but no further pertinent studies were identified.

The complete article was sourced for the six studies identified above. One study [10] was excluded as it was a study of treatment during pregnancy and two studies [8][9] were excluded as infants had to be of 12 or six months age to be entered into the study. The other three studies did not exclude neonates in their methods but the results either gave an age range that did not include neonates or there was no data to suggest recruitment of neonates.

Twenty one systematic reviews were identified by the search but only one remained after the search was limited to age group Newborn: birth to one month. This review [13] did not yield data on the specified age range.

#### Discussion

Although data exists to support the safety profile of artemisinin derivatives for uncomplicated malaria for adults and children [3] there are reservations about use in severe malaria [4] or during pregnancy [6]. The requirement for further safety data has been noted [4]; however, as yet, there have been no studies looking specifically at safety in the neonatal period.

### SUMMARY

At present there is no good data on safety on artemisinin derivatives in the neonatal period.

### REFERENCES

- World Health Organization. WHO expert committee on malaria (20th Report). World Health Organization Technical Report Series 2000;892:i-v:1-74.
- Eckstein-Ludwig U et al. Artemisinins target the SERCA of *Plasmodium falciparum*. *Nature*. 2003;424:957-61
- McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. *Cochrane Database Syst Rev*. 2000;(2):CD000256
- South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005; 366:717-725
- Brewer TG, Grate SJ, Peggins JO, Weina PJ, Petras JM, Levine BS, Heiffer MH, Schuster BG. Fatal neurotoxicity of arteether and artemether. *Am J Trop Med Hyg*. 1994;51(3):251-9
- Assessment of the Safety of Artemisinin Compounds in Pregnancy: Report of Two Informal Consultations Convened by WHO in 2002. <http://www.who.int/tdr/publications/publications/pdf/artemisinin-pregn.pdf>. [Accessed 05/05/05]
- Obonyo CO, Ochieng F, Taylor WR, Ochola SA, Mugitu K, Olliaro P, ter Kuile F, Oloo AJ. Artesunate plus sulfadoxine-pyrimethamine for uncomplicated malaria in Kenyan children: a randomized, double-blind, placebo-controlled trial. *Trans R Soc Trop Med Hyg*. 2003;97(5):585-91
- Smithuis F, van der Broek I, Katterman N, Kyaw MK, Brockman A, Lwin S, White NJ. Optimising operational use of artesunate-mefloquine: a randomised comparison of four treatment regimens. *Trans R Soc Trop Med Hyg*. 2004;98(3):182-92.
- von Seidlein L, Walraven G, Milligan PJ, Alexander N, Manneh F, et al. The effect of mass administration of sulfadoxine-pyrimethamine combined with artesunate on malaria incidence: a double-blind, community-randomized, placebo-controlled trial in The Gambia. *Trans R Soc Trop Med Hyg*. 2003;97(2):217-25.
- Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. 2001;95(4):424-8.
- Moyou-Somo R, Tietche F, Ondoa M, Kouemini LE, Ekoe T, Mbonda E, Nsangou C, Jemea B, Guemkam G. Clinical trial of beta-artether versus quinine for the treatment of cerebral malaria in children in Yaounde, Cameroon. *Am J Trop Med Hyg*. 2001;64(5-6):229-32.
- Thuma PE, Bhat GJ, Mabeza GF, Osborne C, Biemba G, Shakankale GM, Peeters PA, Oosterhuis B, Lugt CB, Gordeuk VR. A randomized controlled trial of artemotil (beta-artether) in Zambian children with cerebral malaria. *Am J Trop Med Hyg*. 2000;62(4):524-9
- Bakshi R, Hermeling-Fritz I, Gathmann I, Alteri E. An integrated assessment of the clinical safety of artemether-lumefantrine: a new oral fixed-dose combination antimalarial drug. *Trans R Soc Trop Med Hyg*. 2000;94(4):419-24