



Improving the availability of artesunate for treatment of severe malaria

Artesunate reduces mortality and should now be the treatment of choice in severe malaria in adults: good news for countries in our region, but registration in Australia must wait

For nearly 400 years quinine has been the principal drug used to treat severe malaria. Despite its long history of efficacy, quinine has significant limitations. Even with prompt administration, case-fatality rates in severe malaria often exceed 20%.¹ Furthermore, quinine requires three-times-daily administration and has a number of adverse effects including hypoglycaemia, vomiting, headache and tinnitus.¹

The identification of artemisinin from sweet wormwood (*Artemisia annua*) in China in the 1970s focused attention on the most rapidly acting of all antimalarial drugs,¹ and raised hopes that artemisinin derivatives would reduce the high case-fatality rate in severe malaria. Initial trials using intramuscular artemether demonstrated less toxicity but no clear mortality benefit over quinine,¹ most likely due to the erratic absorption of the intramuscularly administered oil-based preparation of artemether.^{2,3} More recent trials have used intravenous artesunate, a water-soluble derivative with a more favourable pharmacokinetic profile.^{3,4} The SEAQUAMAT trial, a multicentre randomised trial conducted in Bangladesh, Myanmar, Indonesia and India, recently reported a 34.7% reduction in mortality associated with intravenous artesunate compared with intravenous quinine.⁵ This is the largest trial ever performed in severe malaria and the first to demonstrate conclusively a mortality reduction over standard quinine therapy.

This is good news for malaria-endemic areas in South-East Asia. The burden of malaria in our region is far worse than previously thought, with over 120 million cases each year in south/south-east Asia.⁶ The World Health Organization now advocates the use of artemisinin combination therapy for uncomplicated malaria,⁷ a move that is likely to reduce the number of people developing severe disease. Now there is convincing evidence that for those who do develop severe malaria, intravenous artesunate will reduce the risk of death by one-third.⁵ It is also safer and easier to use than quinine.

What about children? In the 202 children in SEAQUAMAT, artesunate was equally safe and effective.⁵ But the study did not have the statistical power to demonstrate a mortality benefit in the paediatric age group. In the Asian countries that have changed policy, artesunate is first-line treatment for both adults and children. However, because the clinical pattern and rapidity of death is different in paediatric severe malaria in high transmission areas, a randomised trial comparing mortality in African children treated with artesunate and quinine has recently commenced.

Several countries in our region recommend parenteral artemisinin derivatives as first-line therapy for severe malaria, including Vietnam, Thailand, Papua New Guinea and Cambodia.⁸ As a result of SEAQUAMAT, Indonesia has now also changed national policy from quinine to artesunate. However, quinine is still national policy for severe malaria in most other Asia-Pacific countries.⁸

At US\$5c–\$1 per 60 mg vial when purchased in bulk, artesunate is only modestly more expensive than quinine. And this does not take into account the intravenous infusions and additional nursing required for quinine. The number needed to treat to save one life

was between 11 and 20 in the SEAQUAMAT study, making this a very cost-effective policy change.

A major issue for many national bodies faced with licensing parenteral artesunate is that neither of the current manufacturers in China and Vietnam produce a formulation approved as compliant with international Good Manufacturing Practice (GMP) specifications. Support from the developed country pharmaceutical industry does not appear likely. United States Army plans for independently developing a GMP-compliant formulation have been delayed by the lack of a commercial co-development partner.⁹ Absence of GMP certification does not necessarily mean poor quality: independent analysis of the lots used in the SEAQUAMAT trial demonstrated satisfactory quality of this drug. However, neither of the current manufacturers has yet received WHO prequalification certification, a requirement for the WHO and several other international agencies to purchase drugs centrally and distribute large quantities at low cost to ministries of health. Nevertheless, forthcoming WHO guidelines will recommend artesunate be made the treatment of choice for severe malaria in adults.¹⁰

What about Australia and other developed countries? In settings with well resourced intensive care facilities, the mortality rate from severe malaria is less than that seen in most sites involved in the SEAQUAMAT trial.¹¹ It is possible that the benefit with artesunate (seen after 24–48 hours in the SEAQUAMAT trial) could be attenuated by better treatment of late complications in a developed country setting. However, the magnitude of the mortality reduction was remarkably consistent among the SEAQUAMAT sites, despite varying mortalities and levels of ancillary care. Parenteral artesunate should therefore be the treatment of choice for adult severe malaria in all countries.¹⁰ The lack of a GMP-compliant formulation is, however, a major hurdle and means that artesunate cannot be registered in Australia by the Therapeutic Goods Administration¹² or in other countries, including the European Union and United States.

This creates a paradox. In contrast to the usual situation, a life-saving drug is available and being used in many developing countries, yet cannot be registered in developed countries. Although it is clearly far more important that these drugs are available in malaria-endemic countries, and the number of Australians developing severe malaria each year is small, it is unacceptable that we must continue to use quinine when a drug that reduces mortality by one-third is available elsewhere. Pending the availability of a GMP-compliant product that can be registered, an interim strategy is available in Australia. Hospital pharmacies can import and hold artesunate for category A usage in named patients with severe malaria under the Special Access Scheme, reserved for “very seriously ill patients” with a high short-term likelihood of death in the absence of early treatment.¹³ This strategy could be coordinated by a consortium of state/territory hospital pharmacies in capital cities and supported by the relevant national professional bodies. Ideally, the quality of an imported lot of non-GMP

artesunate should have been confirmed at a Good Laboratory Practice-compliant laboratory.

From a global perspective, registration and availability of parenteral artesunate in both malaria-endemic and developed countries would be maximised if current manufacturers were given assistance to become GMP-compliant without delay.

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1 Artemether-Quinine Meta-analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2001; 95: 637-650.

2 Murphy SA, Mberu E, Muhia D, et al. The disposition of intramuscular artemether in children with cerebral malaria; a preliminary study. *Trans R Soc Trop Med Hyg* 1997; 91: 331-334.

3 Hien TT, Davis TM, Chuong LV, et al. Comparative pharmacokinetics of intramuscular artesunate and artemether in patients with severe falciparum malaria. *Antimicrob Agents Chemother* 2004; 48: 4234-4239.

4 Davis TM, Phuong HL, Ilett KF, et al. Pharmacokinetics and pharmacodynamics of intravenous artesunate in severe falciparum malaria. *Antimicrob Agents Chemother* 2001; 45: 181-186.

5 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.

6 Snow RW, Guerra CA, Noor AM, et al. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* 2005; 434: 214-217.

7 Davis TM, Karunajeewa HA, Ilett KF. Artemisinin-based combination therapies for uncomplicated malaria. *Med J Aust* 2005; 182: 181-185.

8 World Health Organization global antimalarial drug policy database, 2005. Available at: http://www.who.int/malaria/amdp/amdp_searo.htm and http://www.who.int/malaria/amdp/amdp_wpro.htm (accessed Nov 2005).

9 Magill A, Panosian C. Making antimalarial agents available in the United States. *N Engl J Med* 2005; 353: 335-337.

10 World Health Organization. Guidelines for the treatment of malaria. Geneva: WHO, 2006. In press.

11 Bruneel F, Hocqueloux L, Alberti C, et al. The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. *Am J Respir Crit Care Med* 2003; 167: 684-689.

12 Australian Government. Therapeutic Goods Act 1989. Available at: <http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/framelogmentattachments/8D8974B9D6A524C6CA256FBF001233C8> (accessed Nov 2005).

13 Therapeutic Goods Administration. Special Access Scheme: access to unapproved therapeutic goods. Canberra: Department of Health and Ageing, 2001. □

A new EPOC in Australian health research

Contributing to health services research, implementation and effective health policy-making

Some of the most pressing issues in Australian health care are not about the efficacy of particular treatments, but rather how health services can be organised to deliver optimal care. Examples of service-related initiatives familiar to most clinicians include:

- multidisciplinary teams to improve coordination of cancer care;
- designated trauma centres to optimise management of injured patients;
- financial incentives to encourage particular services;
- restricted licences for overseas medical graduates to increase the rural workforce;
- specialist outreach and telemedicine to improve access in remote areas;
- clinical audit and review to enhance care quality; and
- management and prescribing guidelines.

Broadly speaking, these represent a spectrum of organisational, financial, regulatory and professional interventions aimed at improving service delivery and achieving best practice.

Just as clinicians and patients are concerned with the effectiveness of clinical treatments, policy-makers and the public are interested in the effectiveness of health system interventions. For clinical treatments, questions about “what works” may be best

answered using randomised controlled trials and other experimental designs. Those studying the effectiveness of health service interventions, however, face some specific methodological and analytical challenges, and often need to consider other types of designs. Is it possible to randomise communities to receive outreach visits, for example? What are the important outcomes of employing nurse practitioners in remote areas? Can we effectively control for other health service changes, such as closure of a hospital, or loss of staff, that may be unavoidable during a study period? In studies in which the intervention is delivered to a population, but the outcomes are measured in individual patients, how do we take clustering effects into account in the analysis?

Australians have contributed to developing appropriate methods (some adapted from economics and social sciences) for addressing such questions in real-world situations. Support for the Australian health services research community has come from the Health Services Research Association of Australia and New Zealand (<http://www.chere.uts.edu.au/hsraanz/>), established in 2001, the long-standing interest of *The Medical Journal of Australia*, as well as other organisations, and the *Australian and New Zealand Journal of Public Health*, *Australian Health Review*, and a new open-access journal,