EDITORIAL

ARTEMESININS FOR SEVERE MALARIA IN AFRICA?

One of the greatest success stories of "traditional medicine" has been the development of the artemesinin drugs from the Chinese herbal remedy, qinghaosu. Quinghaosu, an extract of sweet wormwood (*Artemesia annua*), has been used in China for over a thousand years as a treatment for fevers. It was only in the 1970's that Chinese scientists purified artemesinin and demonstrated its powerful antimalarial properties. This led to the development of a range of drugs based on artemesinin derivatives which found widespread use in China. Its use outside China was initially limited, partly because most of the original literature was difficult to access for researchers elsewhere, and partly because of reluctance on the part of funders in the west to support trials with drugs not manufactured to international standards. However the growing problems of drug resistance, particularly in South East Asia, led to an increase in use of the drugs in that part of the world and eventually to the production of a range of artemesinin derivatives made to international manufacturing standards. The artemesinins provide a good example of the gap between theory and practice in drug regulation. while a number of international panels of experts were earnestly developing policies in the early 1990's to regulate the use of these precious new weapons, the drugs were introduced and registered rapidly in the majority of African countries.

Currently there are a number of oral artemesinins on the market in East Africa, the most commonly used being artemether and dihydro artemether. They have proved popular as rapidly acting antimalarials with few side effects but their use, until recently, has been limited to the private sector by cost. The situation is changing now, with the idea that in order to prevent drug resistance, chemotherapy for malaria, as with HIV or TB, should be with combinations of drugs(1). The rapid action and high effectiveness of the artemesinins make them ideal components of combination therapies and they are likely to play an increasingly important public health role in the first line treatment of malaria.

There has also been increasing interest over the last ten years in the potential of artemesinin drugs in the treatment of severe malaria and the article by Adam *et al.*(2) in this issue is the latest in a series of studies. Several artemesinin derivatives can be used parenterally. Artemether, an oil based intramuscular preparation, is widely available in Africa. Artesunate, a water soluble derivative, is widely used in South East Asia and likely to become increasingly used in Africa over the next few years. As is often the case when new drugs are introduced, initial reports did not produce clear evidence of how well the artemesinin derivatives compared with the standard approach, in this case the use of parenteral quinine. The answer to such problems is nearly always to conduct well randomised trials with large numbers of patients. In the absence of big enough trials, or whilst waiting for them to be completed, a good approach is standardised meta-analysis. This can be either in the form of systematic review of trials or, much more time consuming, meta-analysis using individual patient data. This involves obtaining all the individual patient information from different trials that have been carried out and re-analysing it in a standard fashion. Such an analysis was published in 2001(3) for the use of artemether compared with quinine in the treatment of severe malaria.

The study group(3) identified 11 potential trials, covering children and adults in Africa and South East Asia, in which the two drugs had been compared in a randomised manner. Individual patient data were not available for four small trials but the eventual analysis included 1919 patients, or 86% of all the patients who had ever been in a randomised comparison of the two drugs. For the key outcome measure of mortality there was no significant difference between artemether (14% and quinine 17%), nor for neurological sequelae in the survivors (artemether 10% versus quinine 12%). However there was a significant advantage to artemether when mortality and sequelae were taken together to give a measure of combined adverse outcome (artemether 23%, quinine 27%). Parasite clearance times were consistently faster with artemether (median of 20 hours versus 32 with quinine) but there were no significant differences in coma resolution or fever resolution times. In summary, artemether was at least as effective as quinine in terms of overall mortality and there was a suggestion that it may be more effective with regards to overall outcome. It was easy to use and was associated with fewer serious adverse events.

So should we be switching to use artemether more often in the treatment of severe malaria in East Africa? There remain some issues to consider. Of some concern has been the reports of neurological damage in several animal species given artemesinins, particularly artemether(4). However, clinical experience in South East Asia now involves enormous numbers of patients and no evidence has emerged to date, including in the meta-analysis discussed above, and from detailed histopathological studies, of an equivalent effect in humans. A second concern is that being given as an intramuscular injection in oil, absorbsion might be expected to be variable and least adequate in the sickest patients. There is some evidence that this may be the case, with instances of poor absorbsion reported in the early stage of treatment in a small number of severely ill children(5). A third reason for caution may be the fact that despite the difficulties of using quinine, and its well known side effects, there is enormous experience

in its use, and clinicians and nurses are often rightly reluctant to move away from well established treatments in the absence of a clear advantage for a new therapy. Two factors are likely to lead to increasing use; first is its ease of administration and secondly is the fear of quinine resistance.

We have been remarkably lucky todate not to have quinine resistance emerge as a problem in East Africa. Even now, though anecdotal reports are increasing, there is no clear evidence of significant parasitological resistance, most parasitological failures probably being due to failure to complete a full course. However, we should not be complacent, quinine resistance will likely emerge, quite possibly driven by increasing widespread inappropriate use of incomplete courses to treat none severe malaria.

So at the moment the scales are fairly equally balanced. Artemether is an apparently safe, easy to use and effective alternative to quinine in the treatment of severe malaria in East Africa. However, whichever drug is chosen, it is essential to remember that an antimalarial is only one part of the management of severe malaria and meticulous attention to supportive management which tackles the underlying pathophysiological problems, such as appropriate use of fluids, blood transfusion, correction of hypoglycaemia and anti-epileptics where indicated, are the key to reducing case fatality(6).

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