Major clinical trial prompts call for change to treatment guidelines for severe malaria worldwide

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The largest ever clinical trial in patients hospitalised with severe malaria has concluded that the drug artesunate should now be the preferred treatment for the disease in both children and adults everywhere in the world. The study, funded by the Wellcome Trust, is published today online in the journal *The Lancet*.

An international consortium of researchers, led by Professor Nick White of the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme in Bangkok, Thailand, compared treatment with artesunate, which is used in Asia to treat severe malaria, against quinine, which has been in use worldwide for over three hundred years. The trial – known as the African Quinine v. Artesunate Malaria Trial (AQUAMAT) – was carried out over a five year period in hospitals across nine African countries and studied 5,425 children with severe malaria.

Severe malaria kills nearly a million people each year, mainly young children and pregnant women. It is caused by parasites which are injected into the bloodstream by infected mosquitoes. Severe malaria is often the main reason why children are admitted to hospital in Sub-Saharan Africa, and one in ten of these children die.

For over three centuries, doctors have relied upon the bark of a South American tree to treat tropical fevers. This bark gives quinine, a bitter

medicine used to flavour tonic water, prevent night cramps, and cure malaria. Quinine is a reliably effective drug, but it is difficult to give by injection and has unpleasant side effects, some of which are potentially dangerous.

AQUAMAT compared quinine against the more recent drug artesunate both given either intravenously or by intramuscular injection, and showed that treatment with artesunate reduced the number of deaths from severe malaria by 22.5% compared with quinine. With artesunate treatment 8.5% of the patients died, compared to 10.9% with quinine. The results were very similar in all the study sites.

Children treated with artesunate were also less likely to slip into a deeper coma or have seizures after the treatment was started. Severe hypoglycaemia – dangerously low blood sugar – was also less common in children treated with artesunate. In addition, artesunate was easy to administer, well tolerated, and proved very safe.

Professor White comments: "For over a century, quinine administered by injection has been the best treatment available for treating severe malaria, but thanks to the development of the artemisinin compounds, we now have a safer and much more effective treatment. We recommend that artesunate should now replace quinine for the treatment of severe malaria in both children and adults everywhere in the world."

Artesunate is derived from a Chinese herb called qinghao (Artemisia annua). Nearly forty years ago, Chinese scientists reported that an extract of this herb called was an effective anti-malarial. These reports were treated initially with suspicion but the compounds derived from it (such as artemisinin) have steadily gained acceptance throughout the world. In uncomplicated malaria, artemisinin compounds such as artesunate are now part of the artemisinin-based combination treatments (ACTs) recommended everywhere in the world.

Five years ago the then largest ever trial in patients hospitalized with severe malaria showed that artesunate, given by injection, reduced the death rate compared with quinine. However, this trial was conducted in Asia and most of the patients studied were adults, so there was uncertainty over whether artesunate injection should replace quinine as a treatment of severe malaria in children in Africa, where most of the deaths occur. Today nearly all the children admitted to hospital with severe malaria in Africa still receive quinine.

Dr Arjen Dondorp, Professor White and colleagues from Mahidol University and the University of Oxford, who conducted the original study in Asia, also led the AQUAMAT study. AQUAMAT was carried out in eleven hospitals across Mozambique, Tanzania, Kenya, Uganda, Rwanda, the Democratic Republic of Congo, Nigeria, Ghana, and The Gambia and involved over 200 collaborators. The trial was funded entirely by the Wellcome Trust, a global charitable foundation, and received no funding from the pharmaceutical industry.

Dr Olugbenga Mokuolu from the University of Ilorin in Nigeria, one of the trial collaborating centres, adds: "Severe malaria is a terrible burden on the African continent and across the developing world and we need the best treatments available to combat it. If half of the estimated eight million children annually who suffer from the disease could be treated with injectable artesunate, we could potentially save 100,000 young lives each year. For those of us who treat malaria in Africa, this trial is a turning point. Finally we have a better treatment to offer to our malaria patients."

The trial has been welcomed by Sir Mark Walport, Director of the Wellcome Trust, which supported both the original trial in Asia and the subsequent AQUAMAT study.

"This is an extremely important clinical trial of the treatment of malaria,

showing improved survival of patients with severe malaria in Africa," says Sir Mark. "There are still many hurdles to overcome and we must be vigilant to protect against resistance to these new drugs and against a market in counterfeit drugs. But Professor White and colleagues have shown that we have the potential to save the lives of hundreds of thousands of children."

Provided by Wellcome Trust

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