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Shifting from quinine to artesunate as first-line treatment of severe malaria in children and adults: Saving more lives

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Summary Severe malaria kills more than a half million people each year. Based on high-quality evidence of the efficacy superiority of artesunate over quinine in adults and children with severe malaria, the World Health Organization guidelines have been revised. The WHO currently recommends injectable artesunate as the first-line treatment for severe malaria. Since this revision in April 2011, only a small number of countries affected by malaria have adopted and implemented the new policy. If this policy is implemented, an additional 195,000 lives would be saved each year in Africa. Thus, there is an urgent need to speed up access to injectable artesunate in malaria-endemic countries. This review presents a background for recommending artesunate as the first-line treatment of severe malaria in children and adults, and interventions that are recommended to accelerate access to injectable artesunate.

Introduction

Malaria is a preventable and treatable mosquito-borne disease and a major contributor to morbidity and mortality globally. In 2012, there were an estimated 207 million cases of malaria globally and approximately 627,000 deaths. African children are mostly affected. Approximately 90% of all malaria-related deaths occur in Africa, with 77% being children below five years [1].

Anti-malaria interventions include long-lasting insecticidal nets, indoor residual spraying, intermittent preventive treatment, improved diagnosis using rapid diagnostic tests and adequate treatment of uncomplicated cases using artemisinin combination therapy as first-line therapy [2]. In response to calls for widespread control and

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elimination of malaria and the challenge of meeting the Millennium Development Goals 4 and 6, there has been a rapid scale-up of these interventions [2]. Reducing the mortality due to malaria also requires universal access to appropriate treatment for severe cases. It is estimated that 8 million cases of uncomplicated malaria progress to severe malaria annually [3]. Many affected children die before admission to a hospital or clinic, but for those who are admitted with severe malaria and receive parenteral antimalarial treatment, approximately one in six will die [4]. The policy for first-line treatment of severe malaria is therefore a critical factor in reducing malaria mortality.

Following the emergence of chloroquine-related resistance in the 1970s in South East Asia and Africa, until recently, quinine has remained the standard treatment of severe malaria in Sub-Saharan Africa. In 2011, based on recent high-quality evidence of the efficacy superiority of artesunate over quinine in adults and children with severe malaria, the World Health Organization (WHO) guidelines were revised to recommend injectable artesunate as the first-line treatment for severe malaria in both adults and children [5].

Since the revision of WHO guidelines for the treatment of severe malaria, some African countries have revised their severe malaria treatment guidelines to reflect the WHO recommendation. However, to date, only few countries affected by malaria have adopted and implemented the new policy [1]. Assuming that treating severe malaria with artesunate instead of quinine reduces the risk of death by 39% in adults and 24% in children [6], it is estimated that the use of injectable artesunate as a first-line drug throughout Africa theoretically would save up to an additional 195,000 lives among the estimated 8 million annual cases of severe malaria [3]. Therefore, speeding up access to injectable artesunate in malaria-endemic countries is an emergency. This review presents evidence on the efficacy and safety superiority of artesunate over quinine in adults and children with severe malaria and interventions that have been recommended to accelerate access to injectable artesunate.

Superior efficacy of artesunate over quinine

Parenteral quinine has remained the standard treatment of severe malaria for nearly three decades. The primacy of parenteral quinine in the treatment of severe malaria has been challenged by the introduction of artemisinin derivatives (artesunate, artemether and artemotil). This primacy was established before modern clinical trial methods were developed.

A recent Cochrane meta-analysis including 8 trials compared the efficacy of quinine (comparator) with artesunate (intervention) for severe malaria in endemic settings [6]. This meta-analysis included the two largest trials in children and adults, the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) and the African Quinine versus Artesunate Malaria Trial (AQUAMAT). The primary outcome was all-cause death. The quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach that classifies the aggregate level of quality of evidence into 4 categories: high, moderate, low or very low [7].

Parenteral artesunate significantly reduced the risk of death from severe malaria compared with intravenous quinine both in adults (5 trials, 1664 participants; total events: 124 (artesunate), 198 (quinine); RR 0.61, 95% CI 0.5—0.75; high quality evidence) and in children (4 trials, 5765 participants; total events: 240 (artesunate), 315 (quinine); RR 0.76, 95% CI 0.65—0.90; high-quality evidence). These results indicate that treating severe malaria with artesunate instead of quinine reduces the risk of death by 39% in adults (95% CI 25—50) and 24% in children (95% CI 10—35). Artesunate reduced the frequency of hypoglycemia episodes in children (4 trials, 5765 participants; total events: 54 (artesunate), 87 (quinine); RR 0.62, 95% CI 0.45—0.87; high quality evidence) and in adults (2 trials, 1372 participants; total events: 12 (artesunate), 32 (quinine); RR 0.36, 95% CI 0.19—0.68; high quality evidence). This corresponds to a 45% (95% CI 26—59%) reduction of hypoglycemia episodes during treatment with artesunate. No difference has been demonstrated for the risk of serious neurological sequelae in children at day 28 (1 trial, 4857 participants; total events: 34 (artesunate), 27 (quinine); RR 1.23, 95% CI 0.74—2.03; moderate quality evidence), though artesunate was associated with an increased risk of neurological sequelae at the time of discharge (3 trial, 5163 participants; total events: 101 (artesunate), 72 (quinine); RR 1.36, 95% CI 1.01—1.83; moderate quality evidence) [6]. As clinical sequelae are less common than death, the data suggest an overall benefit from artesunate therapy if mortality and sequelae are considered jointly [8]. In adults, the data also suggest no difference in the risk of neurological sequelae at discharge between the two treatments (1 trial, 1259 participants; total