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REVIEW

Delayed haemolysis after artesunate treatment of severe malaria – Review of the literature and perspective

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Summary Artesunate has replaced quinine as the recommended first-line treatment of severe malaria as it clears parasites faster and lowers mortality. After artesunate's introduction, however, reports of delayed haemolysis have emerged. Typically, this adverse haemolytic event peaks two to three weeks after the acute phase of malaria, and can be severe enough to make blood transfusions necessary in the management of some patients. Delayed haemolysis has been detected in prospective studies in 7–21% of patients treated with artesunate. A confirmed risk factor in travellers is hyperparasitaemia, while additional in malaria-endemic countries young age has been shown to increase risk. The pathophysiology of this phenomenon has not yet been fully elucidated, but may include various combinations of delayed destruction of "pitted" erythrocytes and autoimmune aetiology.

All patients treated with parenteral artesunate should be followed up for at least four weeks to detect signs of haemolysis and to allow appropriate symptomatic treatment.

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1. Introduction

Based on two large multi-national trials, SEAQUAMAT: South-East Asia Quinine Artesunate Malaria Trial; AQUAMAT: Africa Quinine Artesunate Malaria Trial, it has been established that artesunate lowers mortality from severe malaria by approximately a quarter when compared to quinine in malaria-endemic regions [1—3]. In addition to its superior efficacy over quinine, artesunate has been credited with a favourable safety profile. Most importantly artesunate lowers the risk of hypoglycaemia by 45% [3]. While in African children neurological sequelae at hospital discharge were seen more often in those treated with artesunate, this difference did not persist at a follow-up visit after 28 days and could be explained by the higher survival rate of severely ill children [2]. Other known side-effects of quinine and quinidine, such as visual and hearing disturbances or ECG changes have not been observed during or after treatment with artesunate [4,5]. However, evidence regarding adverse events is limited as the large artesunate trials were not specifically designed to assess these [1,2,6]. The reported duration of follow-up was only the length of the initial hospital stay (median: 5 days) in the SEAQUAMAT study. In the AQUAMAT study, only a subset of children without full clinical recovery at discharge were followed up on day 28. No laboratory results have been reported from follow-up visits for either trial.

The shift from quinine to artesunate as drug of choice for treating severe malaria by the WHO in 2006 has led to the use of artesunate not only in endemic settings but also in returning travellers with severe malaria — despite the fact that artesunate is not licensed in any country in the Western world and is available under a full Good Manufacturing Practice (GMP) — conforming formulation only in the United States and Canada [7—9]. The first report of artesunate use in Europe describes nine patients with severe malaria treated in Norway. All patients survived. While no data on follow-up of these patients are available, no adverse events were reported during their hospital stay (median 4 days) [8]. A second case series of 25 patients treated in 7 European centres, characterized six patients who were diagnosed with haemolysis in the second to third week after treatment, a hitherto unreported complication [10]. Zoller et al. described patients with two different patterns of haemolysis: three showed delayed haemolysis with a secondary peak of haemolytic activity two weeks after treatment with artesunate; three other patients presented with persistent haemolysis for a duration of up to four weeks without any normalization or stabilization of haemoglobin or lactate dehydrogenase (LDH) after the acute phase of malaria [10].

In the current review, we appraise the available literature on delayed haemolysis and highlight points that need further research.

We used the queries "artesunate AND haemolysis" and "artesunate AND anaemia" in Pubmed on November 23, 2014 to retrieve relevant literature. Only results in English language were further analysed. The search yielded 11 publications reporting original data on delayed haemolysis after treatment with parenteral artesunate (Table 1).

2. Case definition of delayed haemolysis

A uniform case definition for delayed haemolysis is lacking [11]. During the acute phase of malaria, markers of haemolysis are typically elevated due to the destruction of infected and uninfected erythrocytes as well as due to acute phase reactions. A further cause of malaria-associated haemolysis is blackwater fever (BWF). BWF has so far been seen mainly in patients with low parasitaemia [12]. Furthermore the peak haemolytic activity in BWF occurs earlier after initiation of treatment. In a Vietnamese study the median time between quinine use and haemolysis was 24 h — compared to two to three weeks in delayed haemolysis after artesunate [13].

Hence the case definition for delayed haemolysis has to clearly delimit it from the other manifold causes of malaria-related haemolysis or anaemia seen during acute disease. While in the first reports several patterns of haemolysis have been described, only delayed haemolysis with a secondary peak can be considered as a distinct entity in the context of treatment with artesunate [11]. Prolonged or persistent haemolysis is a phenomenon which has already been described in the past and is not specific to patients treated with artesunate [14]. Accordingly a stringent case definition should include the unique pattern of a secondary peak of haemolytic activity two to three weeks after treatment of severe malaria, as was done in the two available prospective studies on the topic [15,16]. Fig. 1 depicts the typical time course of delayed haemolysis of a case fulfilling the criteria mentioned above.

3. Case reports and case series on delayed haemolysis in travellers returning with severe malaria

After the initial report by Zoller et al. the existence of delayed haemolysis was confirmed in a further retrospective analysis of 68 patients treated with artesunate in a named patients programme in the Netherlands and Belgium. Six out of 20 patients with available data developed delayed haemolysis, while one patient showed persistent haemolysis [17]. In a retrospective study in Hamburg, Germany, we could find signs of delayed haemolysis in two out of four patients who had been treated with rectal artesunate and in three out of four patients who had been treated with intravenous artesunate [4]. Further cases of delayed haemolysis were reported from Italy, France, Great Britain and the United States [9,18—20]. The evidence from these reports led to the general recommendation of following up patients treated with artesunate for up to four weeks after treatment [9,21,22].

A common feature of the majority of cases with delayed haemolysis among travellers was a high initial parasitaemia (range: 4%—37% infected erythrocytes), with the exception of one patient who only had a parasitaemia of 0.8%. Only two out of eleven patients with available information were born in a malaria-endemic country and travelled for visiting friends and relatives (VFR), all others were Caucasian [4,10,18]. However besides the inherent inability to deduce