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**REVIEW ARTICLE** **OPEN ACCESS**

# The Artesunate Overview

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**ABSTRACT**
*AS, a medication, has been shown to be successful in a significant number of clinical trials as a treatment for M. Post-artesunate delayed hemolysis, more often referred to as PADH, is an unusual side effect of treatment for malaria that has the risk of causing injury. The vast majority of PADH patients are not immune travelers. As a consequence of this, we have settled on the idea that, throughout the course of our investigation, we would look at the pharmacokinetic action of AS, as well as its pathophysiology, side effects, implementation and use.*
***Keywords:*** *pharmacokinetic, pathophysiology, side effects, implementation, use, AS, PAD.*

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## INTRODUCTION

Numerous studies have shown that the medication artesunate (AS), is effective against malaria (M).[1] In addition, studies have shown that the intravenous form of quinine is preferred over the oral form in this condition.[1] Frequently, studies have also shown that it is employed as a component of combination therapies such as AS and mefloquine.[2] Additionally, studies have also shown that, "AS can be administered via injection into a vein, injection into a muscle, orally, and via the rectum".[2,3] Furthermore, studies have shown that, "kidney failure requiring dialysis, hemoglobinuria (the presence of hemoglobin in the urine), and jaundice are the most common side effects".[4]Studies have led researchers to the conclusion that AS is a more desirable formulation than AM from a pharmacokinetic perspective, so AC can be given through an IV or an injection into the muscle, and it quickly reaches therapeutic plasma concentrations either way.[5] Studies suggest that AS may be more effective than AM, particularly in light of the fact that AM is comparable to quinine in terms of effectiveness.[6] Thus, in our review we have decided to describe AS .

## AS OVER QUININE (QN)

According to studies, the South East Asian QN AS Malaria Experiment (SEAQUAMAT) Group had concluded that more than 1,500 people were with severe malaria.[7] Furthermore, the study also demonstrated that AS outperformed QN in terms of reducing mortality rates.[7] Hence, the "groundbreaking study provides further support for the notion that AS should be used instead of quinine and quinidine for the treatment of severe malaria in the United States".[7]

## PHARMACOKINETIC

Researchers have found that "esterase-catalyzed hydrolysis breaks down AS to make DHA, which is is an active metabolite. This conversion happens rapidly after AS is administered intravenously, as seen by the swift decrease in AS levels shortly after the dosage is given. Out of the eight studies that evaluated AS PK, the average half-life of AS after intravenous administration was shown to be shorter than five minutes in at least one group of participants in six of those investigations. The average half-life of AS, as calculated in all of the investigations, was found to be less than fifteen minutes".[8] According to the research conducted by Li et al., it was shown that "AS exhibits dose linearity when administered intravenously within a dosage range of 0.5–8 mg/kg".[9] Research has indicated that the "oral bioavailability of DHA was found to be 82% in healthy adults"[10] Studies have also shown that, "85% in adults with uncomplicated falciparum malaria[11] and 80% in adults with vivax malaria".[12] Studies concluded that,it is important to consider that the "bioavailability results may indicate the absorption of AS and its

conversion to DHA through first-pass or systemic metabolism as well as direct absorption of DHA following formation in gut through acid-dependent chemical hydrolysis".[13]

**PATHOPHYSIOLOGY**

Research has shown that artemisinin (AM) and its derivatives are known for containing the endoperoxide group. Research has also found that the "distribution of AM derivatives in a patient's body leads to the cleavage of an endoperoxide bridge. As a result, reactive oxygen species and free radicals are produced".[14] In addition, research has indicated that this harmful waste plays a crucial role in eliminating young malarial parasites, specifically ring-form trophozoites, by effectively hindering their survival within red blood cells. Research has indicated that the powerful and fast-acting erythrocytic schizonticidal effect of AM derivatives against Plasmodium spp. is extremely effective.[15,16,17,18,19] As a result, studies have shown that , "AM derivatives lower the chance of erythrocyte sequestration and slow down the progress of severe malaria".[14] Furthermore, studies have shown that ,once the malarial parasites are dead, the inter-endothelial slits in the spleen remove the parasites from the erythrocytes that still carry the dead parasites.[14,18,19]

**ADVERSE EFFECT**

According to research, AS has the potential to cause major adverse effects, such as hemolytic anemia (a disease in which red blood cells are destroyed) and severe allergic responses.[20] Furthermore,studies revealed that AS has a low risk of adverse effects and is well-tolerated by patients. QN and anti-malarial antibiotic medication are more likely to cause vomiting and tinnitus, while regimens based on AS are less likely to do so.[20] Additionally, studies have concluded that one well-known side effect of artemisinins is a decrease in reticulocyte numbers.[21] Researchers have also found a link between the rising use of intravenous (IV) artesunate and post-artesunate delayed hemolysis (PADH).[22] In addition to this, studies have shown that individuals treated with artesunate for severe malaria had delayed hemolysis (developing around two weeks after therapy).[23]

**USE IN PREGNANCY & CHILDHOOD**

**Pregnancy**

Research has indicated that the administration of AS during the second or third trimesters of pregnancy has not resulted in any documented negative outcomes.[14] According to study, however, the safety of AS during the first trimester of pregnancy has not been established.[14] Research indicates that the World Health Organization (WHO) recommends considering the individual risks and benefits before using artesunate for severe malaria in the first trimester.[14]

**Childhood**

Research has indicated that AS is suitable for pediatric use. It is advisable to refrain from using AS and sulfadoxine/pyrimethamine in newborns due to the potential impact of sulfadoxine/pyrimethamine on bilirubin levels.[24] Studies have concluded that, the "dose of parenteral AS for the treatment of severe malaria in children weighing less than 20 kg should be adjusted to ensure optimal exposure, which may be higher than that of adults".[24] Furthermore, studies have also shown that "AS cannot be administered orally or intramuscularly due to a person's weakness or difficulty swallowing, rectal administration may be used as a pre-referral treatment, provided that parenteral administration is started after transferring the individual to a more advanced facility".[24]

**IMPLEMENTATION**

Even if the risk of post-treatment hemolysis following the administration of these drugs is clearly obvious in a significant percentage of patients, especially non-immune persons, studies have shown that this issue should not be a reason to withhold artesunate or other AS derivatives.[25] Studies have shown that patients who take artesunate or another artemisinin derivative have a much higher risk of developing hemolysis in the post-treatment period. Furthermore, studies have shown that patients treated with artesunate should have weekly follow-up appointments with their doctors to provide easier monitoring and early diagnosis of delayed hemolytic episodes,[18] in addition to doing a complete blood count, serum haptoglobin concentrations, or lactate dehydrogenase concentrations at each visit. Although this illness has not been linked to any fatalities, it has been associated with severe anemia in some patients. However, no known fatalities have been linked to PADH. Because of this, nations without ready access to an adequate supply of safe blood products may see a strain on their healthcare systems.[26] As a result, it is essential to keep an eye out for the diagnosis of PADH, particularly in non-immune persons with a high parasitemia level.[26]

## LITERATURE REVIEW

**Li et al., (2010)** performed a literature review on the use of AS in the treatment of severe and complicated types of malaria and then analyzed the results of the study. They come to the conclusion that progress in the treatment of severe and complicated malaria, both of which are global issues that claim the lives of at least one million people each year, has been mirrored by advances in our understanding of the genesis of severe complications. New medications, such as intravenous AS and intramuscular artemether (AM), are improving patient outcomes and reducing the number of deaths caused by malaria. In clinical trials that compared AM to the traditional parenteral medicine quinine, AM did not show strong evidence of a mortality advantage over quinine. In contrast, quinine was found to be more effective at reducing mortality. The South East Asian Quinine Artesunate Malaria Trials (SEAQUAMAT), a multicenter, randomized, open-label study comparing AS with quinine, showed that parenteral AS was shown to be associated with a 35% reduction in the risk of mortality compared to quinine and is now the recommended treatment by the WHO for severe and complicated malaria in low-transmission areas and in the second and third trimesters of pregnancy, with almost all the benefit reported in those with high parasite counts. Artesunate is a semisynthetic derivative of artemisinin whose water solubility helps absorption and gives it an advantage over other artemisinins since it may be made in oral, rectal, intramuscular, and intravenous forms. Artemisinin is a semisynthetic compound. When AS is digested in a relatively short amount of time, a metabolite known as dihydroartemisinin is generated. Dihydroartemisinin is the most effective schizonticidal metabolite. Injectable AS results in faster systemic availability of AS compared to AM administered intramuscularly. This pharmacokinetic advantage may offer a clinical advantage in the treatment of more severe and complicated types of malaria.[27]

**Kouakou et al., (2019)** conducted a systematic review on the in-depth analysis of the pharmacokinetics of antiretroviral therapy, with a particular focus on the role it plays in the treatment of drug-resistant malaria. They come to the conclusion that the favorable Cav/EC50 ratio for the IV route gives assurance that IV AS will be effective even when there is an increased resistance level. This is the conclusion that they come to. This is the conclusion; they come to the realization. On the other hand, they come to the realization that, in the case of the oral route, a rise in EC50 that is increased by a factor of two may result in the failure of efforts to perform therapeutic procedures. This understanding gives a justification for increasing the oral dosage since it gives a ratio. In order to accomplish the aims of increasing a patient's exposure to their medicine and reducing the risk of the development of resistance, therapeutic drug monitoring in the form of antimalarial stewardship activities is very important. This is very important in light of the fact that there is significant variation in the pharmacokinetics of AS among different patients.[28]

**Kumar et al., (2019)** did original research to evaluate and assess, using a rat model of colon carcinogenesis, whether or not this substance had an inhibitory effect on oxidative stress and inflammation. They discovered that both drugs, in comparison to the experimental control, maintained the histoarchitecture, inhibited cellular influx, reduced the levels of oxidative stress and inflammatory markers, and downregulated cyclooxygenase-2, induced nitric oxide synthase, nuclear factor kappa B, and interleukin 1. They also found that both drugs reduced the levels of oxidative stress and inflammatory markers. They also found that the levels of inflammatory markers and oxidative stress decreased. It was observed that both of these drugs may suppress pro-inflammatory signals as well as oxidative stress, both of which were found to contribute to the development of colon cancer. The degree of protection these drugs offer is comparable, according to the findings. They come to the conclusion that the use of artesunate, much like the use of aspirin, may also lower the incidence of colon cancer and that it has the potential for future investigation for the purpose of treatment. This is something that they say has the potential to be investigated further in the future. This shows that artesunate may have the potential to be used as a treatment in the future.[29]

**Zhang et al., (2022)** did a review article to give an overview of both the known therapeutic effects of artesunate and its possible powerful effects in the treatment of common respiratory disorders. They believe that it works in many ways to help the body fight cancer. These include stopping cells from growing and migrating, controlling the cell cycle, causing programmed cell death, lowering oxidative stress, making blood vessels more permeable, fixing vascular epithelium, stopping tumors from spreading, and making the body more sensitive to main therapy. These are the conclusions that they have come to. After completing in-depth research, they have come to this conclusion. At the moment, a variety of studies have pointed to its potential utility in the treatment of multiple respiratory diseases. In addition, taking into consideration the interaction as well as the extensive variety of pathways that AS

may influence, it is essential to broaden its application range and conduct research into the processes that correspond to it. This is due to the fact that the AS may have an effect on both the interaction and the pathways. In a nutshell, AS has the potential to be employed in the treatment of a wide variety of various respiratory diseases, either as the primary treatment or as an adjuvant therapy. This is the case in both primary and secondary settings.[30]

## CONCLUSION

This review stresses how important it is too closely watch for hemolysis in people who have been treated with artemisinin derivatives, no matter how many parasites they had. It is important for clinicians to understand that PADH can arise from multiple processes, and they should also consider other potential mechanisms and various contributing factors.

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