Mini Review
Volume 10:6, 2021
DOI: 10.37421/mcce.2021.10.170

Malaria Control & Elimination

ISSN: 2470-6965 **Open Access**

Succinct Illustrations of Artesunate Injectables: Clinical Practice

Gudisa Bereda*

Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia

Abstract

Solemn malaria is a medical emergency whose treatment has become accelerated owing to the advent and dissemination of medication-resistant parasites. In plasmodium falciparum malaria, artemisinin kills the gametocytes involving the stage 4 gametocytes, which are differently liable solely to Primaquine. Artesunate is an Artemisinin derivative with extremely good security and efficacy facts for the treatment of solemn malaria. Artesunate is a great fascinating formulation than artemether for pharmacokinetic rationales, as it can be administered either intravenously or intramuscularly, and it reaches therapeutic plasma accumulations hastily when administered by either route. Do not administer artesunate for injection via continuous intravenous infusion. The consummate ubiquitous side effects of Artesunate enclose kidney failure necessitating dialysis, Hemoglobinuria (the presence of hemoglobin in urine) and jaundice. The combinations of artesunate with the dicatecholate iron chelator or with every of the triple hydroxypyridinone iron chelators deferi prone were antagonistic, plausibly as a outcomes of the function of iron in the deed of artesunate.

Keywords: Artesunate • Clinical practice • Injectables •Succinct

Introduction

Solemn malaria is firstly treated parenterally to hastily lesser the level of parasitemia to a non–life-threatening level. A fast downgrade in peripheral parasitemia will also lead to reversal of every coincident organ dysfunction [1, 2]. The pitfall of death from solemn malaria is highest in the initial 24 hrs, yet in consummate malaria endemic countries, the traverse time between referral and arrival at compatible health facilities is ordinarily extended hence detaining the begging of applicable antimalarial treatment, during which time the patient perhaps degenerate or die [3,4]. Solemn malaria sequences from the infection of a high number of RBCs by malaria parasites. Of the 4 species of malaria parasites that infect humans (*P. falciparum, P. vivax, P. ovale, and P. malariae*), nearly entire cases of solemn malaria are owing to *P. falciparum*. Artemisinin, extracted from 'qinghao' or sweet wormwood (*Artemisia annua L.*) which has been segment of traditional Chinese herbal medicine for centuries, was rediscovered and isolated in 1972 by Chinese scientists needing fresh treatments for malaria [5,6]. Artesunate for injection is an antimalarial indicated for the initial treatment of solemn and complicated malaria in adult and pediatric patients. Treatment of solemn malaria with artesunate for injection should consistently be pursued by a complete treatment course of an applicable oral antimalarial regimen [7,8]. When the parasitemia level has being lower to where a patient is capable to cope up with oral medicines, parenteral therapy is ceased and oral antimalarials are bestow to kill entire staying parasites (i.e., to reach heal) [9,10]. Artesunate is a semisynthetic derivative of artemisinin whose water solubility facilitates absorption and furnishes a merit across distinctive artemisinins because it can be prepared as oral, rectal, intramuscular, and intravenous formulations [11, 12]. Artesunate is hastily undergoing hydrolysis to dihydroartemisinin, which is the consummate active schizonticidal metabolite. Injectable AS sequences in a great hasty systemic applicability of AS analogized with intramuscular AM. This pharmacokinetic merit perhaps furnishes a clinical benefit in the treatments of solemn and complicated malaria [13,14] Artesunate, the consummate broadly attainable of the artemisinin-related compounds, is a hemisuccinate derivative of DHA.

Antimicrobial Activity: Artesunate and DHA are active to fight the blood-stage asexual parasites and gametocytes of Plasmodium species involving the chloroquine resistant strains. Although, artesunate and DHA are not active to fight the hypnozoite liver stage figures of *P. vivax and P. ovale* [15-17].

Mechanism of Action: Artemisinin is trusted to respond via its endoperoxide class with haem in *P. falciparum* digestive vacuoles, sequencing in the conformation of free radicals that alkylate parasite proteins. Artesunate is hastily metabolized into an active metabolite DHA. Artesunate and DHA, connate disparate artemisinins consist an endoperoxide bridge that is activated by heme iron leading to oxidative stress, suppression of protein and nucleic acid synthesis, ultra structural alters as well as a de-escalate in parasite growth and survival [18,19]. Both artesunate and DHA are active to fight the otherwise asexual figures of the plasmodium parasites and lucent parasitemia within 48 to 72 hrs [20].

Pharmacokinetics of artesunate: In infected individuals, the elimination half-life of artesunate is around 0.22 hrs. Its active metabolite, DHA, has a delicately lengthy half-life of 0.34 hrs. Collectedly, the average half-life ranges from 0.5 to 1.5 hrs [21]. Because of its short half-life, its use in malaria obviation is restrained. DHA is undergoing metabolism to an inactive metabolite by the liver enzymes CYP2B6, CYP2C19, and CYP3A4 [22].

Preparation of Artesunate for injection for intravenous/ intramuscular administration for the treatment of severe malaria

Constitution: Artesunate for injection must be constituted with the supplied diluent prior to administration. A diluent containing of 12 ml of sterile 0.3 M pH 8.0 Na_3PO_4 buffers is furnished with artesunate for injection. Insert an airway needle into the vial closure to vent the gas which has been generated. Add 5ml of NaCl 0.9% to the reconstituted artesunate vial and mix thoroughly to make a 10mg per ml solution (total volume is 6ml for IV injection). Use 2 ml of 0.9% NaCl to acquire 3 ml of artesunate solution containing 20 mg/mL, for IM injection [23]. Shake the vial thoroughly to dissolve (comparatively 2 to 3 minutes) a substantial quantum of CO_2 gas will be generated and a clear solution should be acquired in three minutes. Parenteral medications products should be examined optically for particulate matter and discoloration prior to administration, whenever solution and container allow. Do not administer artesunate for injection if particulate matter and/or discoloration are remarked [24,25]. After constitution, inject the constituted solution intravenously (through a settled IV line or needle) as a sluggish bolus over

***Address for Correspondence:** Gudisa Bereda, Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia, Tel: +251919622717/+251913118492; E-mail: gudisabareda95@ gmail.com*

***Copyright:** © 2021 Gudisa Bereda. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.*

Received 08 November 2021; **Accepted** 24 November 2021; **Published** 02 December 2021

1 to 2 minutes. Do not administer artesunate for injection via continuous IV infusion. Discard the vial and any unused part of the medicine product after use [24,26]. Storage of the constituted solution: Administers the constituted solution within 1.5 hrs of constitution with the supplemented diluent. The solution should be formulated freshly for every administration and should not be stored [27,28].

Dosage and route of administration: PK surveys in pediatric with solemn malaria taking IM artesunate imply that there is underexposed relatively to older pediatric and adults to both artesunate and the biologically active metabolite DHA in young pediatric. Body weight has also been distinguished as a substantial covariate in surveys of oral and rectal artesunate PKs. As absorption of IM articulate is fast and trustworthy this implies that young pediatric have a high presumed volume of distribution for both compounds, and thereupon seeks a delicately greater dose of parenteral articulate to reach correspondent vulnerabilities to older pediatric and adults [29]. The recommendation was hence modified as: In pediatric less than or equal to twenty kilograms bestow 3mg/kg/dose of injectable at 0, 12 and 24 hrs. and proceed once quotidian until oral administration is reasonable. In pediatric with weight greater than twenty and adults bestow 2.4 mg/kg/dose injectable articulate at 0, 12 and 24 hrs. and proceed once quotidian until oral administration is attainable [30]. Articulate should be preferred to IV quinine, owing to its immediate applicability. Use articulate 2.4 mg/kg IV bolus on admission and repeat at 12 hrs and 24 hrs, then once daily until oral therapy is implicit. When the patient is capable to cope up with oral therapy, bestow a full regimen of artemether + lumefantrine 20mg/120mg – i.e. 6 doses of 4 tablets (total regimen of 24 tablets) bestowed across a period of 60 hrs, as for uncomplicated *P. falciparum malaria*. ACT "to de-escalate the number of parasites during the first 3 days of treatment (decrement of parasite biomass), while the function of the colleague medication is to remove the staying parasites (heal)" [31]

Indications: Treatment of solemn or complicated malaria and foremost treatment of uncomplicated malaria, when continuous vomiting precludes oral therapy, known chloroquine sensitive strains of *P. vivax, P. malariae, P. ovale*; radical treatment for *P. vivax or P. ovale* infections; MDR-P *Falciparum Malaria* [32].

Adverse drug reactions: The consummate ubiquitous side effects enclose kidney failure seeking dialysis, reversible elevation of serum transaminases; hemoglobinuria (the presence of hemoglobin in urine) and jaundice. Artesunate is universally well bearable. Side effects perhaps involve a sluggish heartbeat, dizziness, and small white blood cell levels, GI disturbances, headache, fever, muscle and joint pain, pruritus; seldom rash, detained haemolytic anaemia (occurring 2 to 3 weeks after treatment, specifically in case of hyperparasitaemia and in young pediatric) [33].

Pregnancy: Artesunate is pregnancy category C, so either inquests in animals have displayed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no restrained inquests in women or inquests in women and animals are not avail. Medications should be accustomed solely if the implicit merit maintains the implicit peril to the fetus or the survey in animal model displayed slight pitfall to the pregnant animal, but there is no confirmation in fetal peril of human survey in pregnant women. The WHO recommends that artesunate use for solemn malaria in the 1st trimester should be based on the individual perils versus benefits [34].

Lactation: Even DHA on the breastfed infant or on milk secretion; but its usage is likely acceptable during breastfeeding.

Pediatric: Artesunate is securing for use in pediatric. Artesunate + sulfadoxine/pyrimethamine should be avoided in the newborns owing to sulfadoxine/pyrmethamine consequences on bilirubin. Parenteral artesunate dosing for treatment of solemn malaria in pediatric < 20 kg should be greater than that of adults in order to escalate vulnerability.

Geriatric Use: Clinical surveys of artesunate for injection did not involve adequate numbers of patients aged 65 years and older to detect whether they answered variably than younger patients [35].

Contraindications: Artesunate is generally a well-bearable medication. Known contraindications involve a subsequent solemn allergic reaction to artesunate, such as anaphylaxis.

Drug interactions: Medications that should be restricted while on artesunate are the medicines that suppress the liver enzyme CYP2A6. These involve amiodarone, desipramine, isoniazid ketoconazole, letrozole, methoxsalen and tranylcypromine [34-36]. Strong UGT inducers: concomitant use of artesunate for injection with oral ritonavir, nevirapine, or UGT inducers perhaps de-escalate DHA AUC and C max, which perhaps downgrade the efficacy of artesunate for injection. Strong UGT Inhibitors: concomitant use of artesunate for injection with UGT inhibitors (e.g., axitinib, vandetanib, imatinib, diclofenac) perhaps escalate DHA AUC and C max, which perhaps escalate DHA, consociated adverse reactions. The combinations of artesunate with the dicatecholate iron chelator or with every of the triple hydroxypyridinone iron chelators deferiprone were antagonistic, plausibly as an outcome of the function of iron in the deed of artesunate [37].

Conclusion

Solemn malaria stays a major across-the board health knot and, despite develops in suppression, it is likely to stay so for the forecast in futurity. Artesunate is hastily undergoing hydrolysis to DHA, which is the further active schizonticidal metabolite. Injectable administration of artesunate sequences in a further fast systemic applicability of AS analogized with IM AM. AS is used to treat adults and pediatric with solemn malaria with IV or IM artesunate for at least 24 hrs (involving infants, pregnant women in all trimesters, and lactating women). Pediatric weight < 20 kg should take a greater dose of artesunate (3 mg/kg/dose) than larger pediatric and adults (2.4 mg/kg/dose) to guarantee same medication vulnerability. Administer the constituted solution within 1.5 hrs of constitution with the supplied diluent. The solution should be formulated newly for every administration and should not be stored.

References

1. White J. Nicholas "Anaemia and malaria". *J Malaria* 17 (2018):1-7.
2. Varo Rosauro, Valerie M. Crowley, Antonio Sitoe and Lola Madrid, et al. "Adjunctive therapy for severe malaria: a review and critical appraisal". *J Malaria* 17 (2018):1-8.
3. Mousa Andria, Aana Al-Taiar, Anstey N Joseph and Chaya Badaut, et al. "The impact of delayed treatment of uncomplicated P. falciparum malaria on progression to severe malaria: A systematic review and a pooled multicentre individual-patient meta-analysis". *PLoS medicine* 17(2020):e1003359.
4. Laís Pessanha de Carvalho, Andrea Kreidenweiss and Jana Held. "The preclinical discovery and development of rectal artesunate for the treatment of malaria in young children: A review of the evidence". *Expert Opinion on Drug Discovery* 16(2021):13-22.
5. Mahfouz Ahmad Al-Agroudi, Laila Abd El-Mawla Megahed, Lawrence Tia Banda And Tosson Aly Morsy. "An overview on malaria in sub-saharan with special reference to Tanzania". *J Egyp Soci of Parasitol* 47(2017):273-92.
6. Kenneth Ikenna Onyedib, Michael O. Iroezindu, Emmanuel Tumininu Obishakin and Mark Okolo Ojogba, et al. "Plasmodium knowlesi Infection: Should Africa is prepared for a New Human Malaria Threat?" *International J Tropi Dis Health* 14 (2016):1-2.
7. Aung Pyae Phyo, Kyaw Kyaw Win , Aung Myint Thu and Lei Lei Swe , et al. "Poor response to artesunate treatment in two patients with severe malaria on the Thai–Myanmar border". J Malaria (2018):1-5.
8. Lalloo G. David, Delane Shingadia, David J. Bell and Christopher JM Whitty, et al. "UK malaria treatment guidelines 2016". J Infec 72 (2016):635-49.

9. Burrows J N, Duparc S, Gutteridge WE, van Huijsduijnen RH, et al. “New developments in anti-malarial target candidate and product profiles”. *J Malaria* 16(2017):1-29.
10. Jeremy N. Burrows, Stephan Duparc, Winston E. Gutteridge and Rob Hooft van Huijsduijnen, et al. “New developments in anti-malarial target candidate and product profiles”. *J Malaria* 16(2017):1-29.
11. Dwivedi Pankaj, Renuka Khatik Kiran Khandelwal and IshaTaneja, et al. “Pharmacokinetics study of arteether loaded solid lipid nanoparticles: an improved oral bioavailability in rats”. *Inter J pharma* 466 (2014):321-7.
12. Chinaeke EE, SA Chime, VI Onyishi and AA Attama, et al. “Formulation development and evaluation of the anti-malaria properties of sustained release artesunate-loaded solid lipid microparticles based on phytolipids”. Drug delivery 22(2015):652-665.
13. Adebayo JO, Tijjani H, Adegunloye AP, Ishola AA, et al. “Enhancing the antimalarial activity of artesunate”. *Parasit Res* (2020):1-6.
14. Gangil Jeetu and Bhaswat S. Chakraborty. “Evaluation of Efficacy and Safety of Artemisinin Derivatives Comparison with Quinine in Paediatric Population for Treatment of Severe Malaria: A Meta-Analysis Approach”. *Intern J Pharma Sci Drug Res* 10(2018):85-94.
15. Luiz C S Pinheiro, Lívia M Feitosa, Flávia F DA Silveira and Nubia Boechat . “Current antimalarial therapies and advances in the development of semi-synthetic artemisinin derivatives”. Anais da Academia Brasileira de Ciências 90(2018):1251-71.
16. Ellis M Katherine, Leonardo Lucantoni, Marina Chavchich and Matthew Abraham, et al. “The novel bis-1, 2, 4-triazine MIPS-0004373 demonstrates rapid and potent activity against all blood stages of the malaria parasite”. *Antimicro Agents Chemo* (2021):311.
17. Singh Sajo, Amish Singh, Mahesh Singh, Dado Soo, et al. “Modern advancement in the area of antimalarial drug development”. *J Heterocycl Chem* 28(2018):185-93.
18. Crespo-Ortiz M Pinnaco and Wei M Qrantin. “Antitumor activity of artemisinin and its derivatives: from a well-known antimalarial agent to a potential anticancer drug”. *J Biomedi and Biotech* (2012).
19. Boechat Nisha, da Silva Pinheiro LC and da Silveira FF. “Antiplasmodial activity”. *J In Sesquit Lacto* (2018):197-221.
20. Wojnarski Mariusz, Chanthap Lon, Pattaraporn Vanachayangkul and Panita Gosi, et al. “Atovaquone-proguanil in combination with artesunate to treat multidrug-resistant P. falciparum malaria in Cambodia: an open-label randomized trial”. *In Open forum infectious diseases* 6 (2019):314.
21. Morris C Anasa, Duparc Sidu, Borghini-Fuhrer Isha and Jung Dayo, et al. "Review of the clinical pharmacokinetics of artesunate and its active metabolite dihydroartemisinin following intravenous, intramuscular, oral or rectal administration". *J Malaria* 10(2011): 263.
22. Hess Karl Manish, Goad Jeffery Aayrajh and Arguin Paul Miskn. "Intravenous Artesunate for the Treatment of Severe Malaria". *Annals of Pharmaco*. 44 (2010): 1250-1258.
23. Booker A Linu and Protocol Sahil. “Phase II Study of Sorafenib Plus 5-Azacitidine for the Initial Therapy of Patients with Acute Myeloid Leukemia and High Risk Myelodysplastic Syndrome with FLT3-ITD Mutation” *J Malaria* (2014): 76.
24. Strickley G Robert .“Pediatric oral formulations: an updated review of commercially available pediatric oral formulations since 2007”. J Pharma Sci 108(2019):1335-65.
25. Plewes Kinu, Leopold S Johad, Kingston H Wingo and Dondorp A Miyan. “Malaria: what’s new in the management of malaria?” *Infect Dis Clin* 33(2019):39-60.
26. Byakika-Kibwika Pauline, Jane Achan, Mohammed Lamorde and Carine Karera-Gonahasa, et al. “Intravenous artesunate plus Artemisnin based Combination Therapy (ACT) or intravenous quinine plus ACT for treatment of severe malaria in Ugandan children: a randomized controlled clinical trial”. *BMC infec dis* 17(2017):1-9.
27. Vreden SGS , Bansie RD, Jitan JK and Adhin MR. “Assessing parasite clearance during uncomplicated Plasmodium falciparum infection treated with artesunate monotherapy in Suriname”. *Infec drug resis* 9(2016):261.
28. Soltanifar Daniel MBBS, Brendan Carvalho MBBCh and Pervez Sultan MBChB . “Perioperative considerations of the patient with malaria”. *J Anesth/J canad d'anesth* 62(2015):304-18.
29. Finku Bruneel, Raffetin Anagi, Corne Piyush, Llitjos J Fopinj, et al. “Management of severe imported malaria in adults”. *J Medi maladi infect* 50(2020):213-25.
30. Osarfo Joseph, Harry Tagbor, Matthew Cairns and Michael Alifrangis, et al. “Dihydroartemisinin-piperaquine versus artesunate-amodiaquine for treatment of malaria infection in pregnancy in Ghana: an open-label, randomised, non-inferiority trial”. Trop Medi Interna Health 22(2017):1043-52.
31. Burger J Renée, Benjamin J. Visser, Martin P. Grobusch and Michèle van Vugt. “The influence of pregnancy on the pharmacokinetic properties of artemisinin combination therapy (ACT): a systematic review”. J Malaria 15(2016):1-36.
32. Marangoni Franca, Irene Cetin, Elvira Verduci and Giuseppe Canzone, et al. “Maternal diet and nutrient requirements in pregnancy and breastfeeding”. *Nutri* 8(2016):629.
33. Kazi M Jamil , Rashidul Haque, Ridwanur Rahman and M Abul Faiz, et al. “Effectiveness study of paromomycin IM injection (PMIM) for the treatment of visceral leishmaniasis (VL) in Bangladesh”. *PLoS negle tropi dis* 9(2015):e0004118.
34. Eugene G Hrycay and Stelvio M Bandiera. “Cytochrome P450 enzymes. Preclinical development handbook: ADME and biopharmaceutical properties” *J Bio pharm* (2008):627-96.
35. Xing Jie, Brian J Kirby, Dale Whittington and Yakun Wan, et al. “Evaluation of P450 inhibition and induction by artemisinin antimalarials in human liver microsomes and primary human hepatocytes”. Drug Meta Dispos 40(2012):1757-64.
36. Bell Angus. “Antimalarial drug synergism and antagonism: mechanistic and clinical significance”. FEMS Micro letters 253(2005):171-84.
37. Santos ALS, CL Sodre, RS Valle and BA Silva, et al. “Antimicrobial action of chelating agents: repercussions on the microorganism development, virulence and pathogenesis”. Cur Medi Chem 19(2012):2715-2737.

How to cite this article: Gudisa Bereda. "Succinct Illustrations of Artesunate Injectables: Clinical Practice." *Malar Contr Elimination* 10 (2021): 170.