Artesunate; MOA, Dosing, Indications, Interactions, Side effects

Artesunate is an antimalarial that is an hemisuccinate derivative of dihydroartemisinin which is itself formed by the reduction of artemisinin.
Artemisinin is a sesquiterpene lactone endoperoxide, that has been for years used in the Republic of China as an antipyretic.

Artesunate together with artemether and dyhydroartemisinis are most important analogs of artemisinin.

Artesunate is water-soluble; useful for oral, intravenous, intramuscular, and rectal administration. Intravenous artesunate was made available by the CDC in 2007; Artemisinin and its analogs are very rapidly acting blood schizonticides against all human malaria parasites. Artemisinins have no effect on hepatic stages.

Mechanism of action of artesunate

The mechanism of action of the Artemisinins likely involves the iron-catalyzed cleavage of the internal endoperoxide bridge in the parasite food vacuole through the reaction with heme within the infected erythrocyte thereby generating free radicals which alkylate vital parasite proteins.

Artemisinin derivatives are concentrated in the parasitized erythrocytes and it is believed that iron from ingested hemoglobin of the parasite's victim reduces endoperoxide bridge releasing a highly reactive free radical iron(IV) oxo species that rips apart the parasitic cells.

However artemisinin has also been reported to work by inhibiting essential parasite calcium adenosine triphosphate (calcium ATPase.)

Pharmacokinetics

After an intravenous injection, artesunate is **rapidly biotransformed** to its active metabolite known as dihyroartemisinin (DHA).

Following a single intravenous dose of 2.4 mg/kg, the maximum artesunate concentration in plasma (Cmax) is estimated to be 77micromols per liter in cases of severe malaria and 36-42 micromols per liter in uncomplicated malaria.

Artesunate is **rapidly absorbed** following intramuscular administration and peak plasma levels are achieved within 30 minutes of administration.

Distribution; plasma protein binding of dihydroartemisinin was determined to be 93% in patients and 88% in healthy volunteers.

Artemisinin and its analogs are rapidly absorbed, with peak plasma levels occurring in 1–2 hours.

Artesunate half life is about 5 minutes

Drug levels appear to decrease after a number of days of therapy.

Metabolism and elimination;

Artesunate is extensively and rapidly hydrolyzed by the plasma esterases enzymes with positive minimal contribution by the cytochrome 2A6.

The main metabolite, dihydroartemisinin accounts for most of the in vivo antimalarial activity of oral artesunate.

Dihydroartemisinin is further metabolized n the liver by glucronidation and its excreted n urine.

Alpha dihydroartemisinin beta glucronide is the major urinary product in patients with falciparum malaria.

Indications of artesunate

Artesunate is indicated in the treatment of severe malaria that has been caused by plasmodium falciparum in adults and children.

The WHO recommends five artemisinin-based combinations for the treatment of uncomplicated falciparum malaria

Intravenous artesunate also has a superior side-effect profile compared with that of intravenous quinine or quinidine

Artesunate has also been effective in the treatment of severe malaria when rectally administered.

Contraindications

Artesunate is contraindicated in patients who are allergic to artesunate , other artemisinins or their derivatives or any of their ingredients.

Precautions

A precaution should be taken when administering artesunate to patients with hepatic or renal impairment and in patients with a slight rise in SGOT and SGP.

Artesunate has not been evaluated for the treatment of severe malaria that has been caused by plasmodium vivax, ovale or plasmodium malariae.

Prevalence of malaria resistance should be considered in choosing an appropriate combination of an antimalarial with artesunate.

Dosage and administration

Artesunate is designed to be administered intravenously of intramuscularly.

In adults and children who are more than 20 kilograms body weight, artesunate is administered at a dosage of 2.4 mg per kilograms body weight by intravenous or intramuscularly at 0, 12 and 24 hours and once a day till oral treatment can be substituted.

In children who are below 20 kg body weight, artesunate is administered at a dose of 3 mg per kilogram body weight intravenously or intramuscularly at 1, 12 and 24 hours and then once daily until oral treatment can be substituted.

Artesunate should be administered for a minimum of 24 hours that is three doses regardless of the patient's ability to tolerate oral medication earlier.

Artesunate Combinations

- Artesunate-sulfadoxine
- Artesunate-mefloquine
- Artesunate-amodiaquine

Reconstitution of artesunate

Step 1
The powder for injection should be reconstituted with 1 ml of 5% sodium bicarbonate and shaken vigorously until the solution becomes clear.

Step 2
For intravenous use, add 5 ml of normal saline or 5% dextrose and for intramuscular use you need to add 2 ml of normal saline or 5% dextrose and mix again.

Step 3
For intravenous use, the required amount of the drug is administered over a period of 2-3 minutes.

The powder for injection is difficult to dissolve and care should be taken to ensure that it is completely dissolved before parenteral administration.

It should be always be used immediately after reconstitution.

If the solution is cloudy or a precipitate is present the parenteral preparation should be discarded.

Side effects

Artesunate and other artemisinin derivatives are usually well tolerated and are associated with minimal side effects, when they occur, the common ones are;

Transient abdominal pain, diarrhea, tinnitus, lightheadedness, dizziness, headache, insomnia cough, nasal symptoms, altered taste, vomiting, rash, alopecia, athralgia, muscle disorders, fever, malaise and pain at injection sites.

Other uncommon side effects are; neutropenia, anemia,hemolysis, aplasia,allergic reactions,

neuropathy, pancteatitis or elevated liver enzymes or hepatitis.

These complains are most likely to be associated with the underlying malaria other than the drug itself.

Pregnancy and lactation

Severe malarious is usually and emergency n pregnancy, therefore a full dose of a parenteral antimalarial should be administered without delay

Although there has been limited clinical experience with the use of artesunate in pregnancy and lactation.

WHO recommends the use of artemisinin-based combination for the treatment of uncomplicated falciparum malaria during the second and third trimesters of pregnancy, intravenous artesunate or quinine for the treatment of severe malaria during the first trimester, and intravenous artesunate for treatment of severe malaria during the second and third trimesters.

In general cases, parenteral artesunate may be used in patients during pregnancy and lactation under medical supervision only if benefits to the mother outweight the risks to fetus of the child.

Interactions

The elimination of artesunate metabolites is rapid hence the potential for drug-drug interaction is limited.

In vitro drug interaction studies have shown minimal effects of artesunate pn cytochrome P450 enzymes.

Overdose

Experience of an acute artesunate overdose is limited. the overdose may be associated with pancytopenia, melena, and seizures.

Symptomatic treatment should be initiated for the effects occured sue to side effects.