Halofantrine

Class:
Halofantrine is related structurally to quinine and other quinoline-containing blood schizonticides such as chloroquine and mefloquine.

Antiparasitic Activity:
Halofantrine is effective against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. Its principal plasma metabolite, *N*-desbutylhalofantrine, is also active against sensitive and resistant parasites.

Mechanism of Action:
Halofantrine may share the same mechanism(s) of action as the 4-aminoquinolines since it forms a complex with ferriprotoporphyrin IX *in vitro* and interferes with the degradation of haemoglobin.

Mechanism of Resistance:
Allelic exchange experiments in the *pfmdr1* gene show that changes in Pgh1 can modulate resistance to halofantrine.

Pharmacokinetics:
Absorption of halofantrine is poor and bioavailability is low. There is wide intra- and inter-subject variability.
Halofantrine is bound to low- and high-density lipoproteins in human plasma.
The elimination half-life of halofantrine after intravenous administration to malaria patients is 14.4 hours. In convalescence, this value is reduced to 7.5 hours.
This value is prolonged in patients with malaria (91-103 hours).

Dosage:
For adults (<40kg) 3 doses of 500mg (2 x 250mg tablets; 8mg/kg) every six hours

Pregnancy:
Halofantrine should not be given in pregnancy unless there is a strong indication.

Adverse Effects:
The most serious effects of halofantrine relate to QTc prolongation, episodes of torsades de pointes or sudden cardiac death. These effects are related to the circulating plasma concentrations of halofantrine and can occur with therapeutic dosages.
Pretreatment with mefloquine appears to exacerbate these effects, due possibly to a pharmacokinetic interaction between the two compounds.

Drug Interactions:
The absorption of halofantrine can be increased dramatically when taken with food.
Both *C*<sub>max</sub> and AUC of halofantrine and desbutylhalofantrine are increased by an order of magnitude after the administration of a 250 mg dose with a fatty meal.