ARTEMETHER BIOAVAILABILITY AFTER ORAL OR INTRAMUSCULAR ADMINISTRATION IN UNCOMPLICATED FALCIPARUM MALARIA


The antimalarial activity of artemether following oral or intramuscular administration in the plasma of 15 adults with acute uncomplicated *Plasmodium falciparum* malaria was measured by bioassay. The peak concentrations in plasma following oral administration were higher in patients with acute illness (median, 1,905 mmol of dihydroartemisinin [DHA] equivalents per liter; range, 955 to 3,358 mmol of DHA equivalents per liter) than in patients in the convalescent phase (median, 955 mmol of DHA equivalents per liter; range, 576 to 1,363 mmol of DHA equivalents per liter), and clearance (CL/F) was lower in patients in the acute phase (1.11 liters/kg/h; range, 0.21 to 3.08 liters/kg/h) than in patients in the convalescent phase (median, 2.76 liters/kg/h; range, 1.56 to 5.74 liters/kg/h) (*P* ≤ 0.008). Antimalarial activity in terms of the peak concentration in plasma (*C*<sub>max</sub>) after oral administration was a median of 16 times higher than that after intramuscular administration. The ratio of the area under the plasma concentration-time curve during the first 24 h (*AUC*<sub>0-24</sub>) after oral administration of artemether to the *AUC*<sub>0-24</sub> after intramuscular administration was a median of 3.3 (range, 1 to 11) (*P* = 0.0001). In the acute phase, the time to *C*<sub>max</sub> was significantly shorter after oral administration (median, 1 h; range, 0.5 to 3.0 h) than after intramuscular administration (median, 8 h; range, 4 to 24 h) (*P* = 0.001). Intramuscular artemether is absorbed very slowly in patients with acute malaria.


ASSESSMENT OF THE NEUROTOXICITY OF ORAL DIHYDROARTEMISININ IN MICE

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High doses of the oil soluble antimalarial artemisinin derivatives artemether and arteether given by intramuscular injection to experimental mammals produce an unusual pattern of selective damage to brain stem centres predominantly involved in auditory processing and vestibular reflexes. We have shown recently, in adult Swiss albino mice, that constant exposure either from depot intramuscular injection of oil-based drug, or constant oral intake carries relatively greater neurotoxic potential than other methods of drug administration. Using the same model, oral dihydroartemisinin was administered once daily at different doses ranging from 25-300 mg/kg/day for 28 days. The neurotoxic potential of the oral dihydroartemisinin was assessed and compared to the oral artemether and artesunate. Oral artemether, artesunate, and dihydroartemisinin had similar neurotoxic effects with no significant toxicity at doses below 200mg/kg/day. These data indicate that once and twice daily oral administration of