

ARTEETHER-INDUCED INJURY TO THE SUBSTANTIA NIGRA IN THE *RHESUS* MONKEY

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The artemisinin compounds arteether (AE) and artemether (AM) have been studied for their effectiveness in the treatment of severe *falciparum* malaria. Arteether- and AM-induced neurotoxicity was observed previously in rats, dogs, and *Rhesus* monkeys. This report continues to evaluate the extent of AE-induced neurotoxicity in the *Rhesus* monkey. A preeminent neuropathological feature of paralysis agitans (Parkinson's disease) is the loss of neurons in the substantia nigra (SN) and the de-pigmentation of neurons in the SN pars compacta. The substantia nigra is divisible into 1) the pars compacta (SNc) containing dopamine and melanin-rich neurons, and 2) the pars reticularis (SNr) rich in gamma-aminobutyric acid (GABA) and glutamic acid decarboxylase (GAD). The connections of the SN are numerous and include afferents from the basal ganglia (caudate, putamen, and globus pallidus), the subthalamic nuclei of Luys, the pedunculopontine nuclei, and raphe nuclei. Nigrostriatal dopaminergic efferent fibers project to the caudate and putamen. The striatonigral (GABA containing) fibers originate principally in the caudate and putamen and terminate in the SNr. Additional projection stem from the external segment of the globus pallidus. Lesions of the substantia nigra lead to hypertonia. A loss of neurons in the SN would result in the degeneration of the prominent nigrostriatal connections. Male *Rhesus* monkeys (*Macaca mulatta*) were administered daily IM doses of the antimalarial drug arteether (AE) at either 24, 16, or 8 mg/kg/d for 14 days, while the 7-day arteether group received either 24 mg/kg/d or 8 mg/kg/d. Control monkeys in the 14-day and 7-day treatment groups received IM USP sesame oil vehicle alone. Surgical anesthesia, exsanguination euthanasia, and perfusion fixation of the central nervous system followed. Brain transverse serial sections were stained according to the methods of Nissl, Kluver-Barrera, and hematoxylin & eosin. Neuropathology was found in neurons of the substantia nigra at all doses in 14-day monkeys and was characterized by: i) central chromatolysis, ii) cytoplasmic eosinophilia, and iii) karyopyknosis, or iv) neuronal loss in some cases. No evidence of neuronal pathology was found in control monkeys in the 14-day group nor in the 7-day treatment group. Adult human with severe *falciparum* malaria were administered intramuscular doses of artemether, as reported previously, at an initial dose of 4 mg/kg followed by a maintenance dose of 2 mg/kg given every eight hours (6 mg/kg daily) for a period of no less than 72 hours. This was effective in treating severe *falciparum* malaria. The risk of injuring the substantia nigra is unquestionable when AE is administered daily for a period of 14 days at doses between 24 - 8 mg/kg.

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