

Toxicity in Rhesus Monkeys Following Administration of the 8-Aminoquinoline 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (WR242511)

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ABSTRACT

Introduction: Many substances that form methemoglobin (MHb) effectively counter cyanide (CN) toxicity. Although MHb formers are generally applied as treatments for CN poisoning, it has been proposed that a stable, long-acting MHb former could serve as a CN pretreatment. Using this rationale, the 8-aminoquinoline WR242511, a potent long-lasting MHb former in rodents and beagle dogs, was studied in the rhesus monkey for advanced development as a potential CN pretreatment.

Methods: In this study, WR242511 was administered intravenously (IV) in 2 female and 4 male rhesus monkeys in doses of 3.5 and/or 7.0 mg/kg; a single male also received WR242511 orally (PO) at 7.0 mg/kg. Health status and MHb levels were monitored following exposure.

Results: The selected doses of WR242511, which produced significant methemoglobinemia in beagle dogs in earlier studies conducted elsewhere, produced very little MHb (mean <2.0%) in the rhesus monkey. Furthermore, transient hemoglobinuria was noted approximately 60 minutes postinjection of WR242511 (3.5 or 7.0 mg/kg), and 2 lethalties occurred (one IV and one PO) following the 7.0 mg/kg dose. Myoglobinuria was also observed following the 7.0 mg/kg dose. Histopathology analyses in the 2 animals that died revealed liver and kidney toxicity, with greater severity in the orally-treated animal.

Conclusions: These data demonstrate direct and/or indirect drug-induced toxicity. It is concluded that WR242511 should not be pursued as a pretreatment for CN poisoning unless the anti-CN characteristics of this compound can be successfully dissociated from those producing undesirable toxicity.

Keywords: 8-aminoquinolines, WR242511, rhesus monkeys, toxicity, pretreatment

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