We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

3,800
Open access books available

116,000
International authors and editors

120M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

Interested in publishing with us?
Contact book.department@intechopen.com

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Pharmacokinetic (PK) and Pharmacodynamic Profiles of Artemisinin Derivatives Influence Drug Neurotoxicity in Animals

Qigui Li and Mark Hickman
Division of Experimental Therapeutics
Walter Reed Army Institute of Research,
Silver Spring, MD,
USA

1. Introduction

In the past decade, there have been major advances in our knowledge of severe CNS neurotoxicity in mice, rats, dogs, and rhesus monkeys repeatedly administered the oil-soluble artemisinins (ARTs) of arteether (AE) or artemether (AM), and water-soluble artelinic acid (AL). Studies have shown that those drugs are toxic to the central nervous system and induce neuropathologic changes in these animals (Li & Hickman, 2011). Pharmacokinetic and toxicokinetic studies of model animals administered various artemisinin derivatives through different routes have yielded important information that is relevant and useful in predicting possible neurotoxicity in man, particularly as artemisinin drugs are used more widely for other indications beyond malaria treatment such as cancer therapy.

The fat soluble artemisinin derivatives AE and AM are particularly prone to induce neuropathological damage at low doses. For example, in rats, CNS damage was induced by dosing with AE intramuscularly at a daily dose of 12.5 mg/kg for 7 days, while a daily dose of 6 mg/kg for 28 days was required to induce neuropathological changes in dogs, and dosing of 8 mg/kg daily for 14 days was required to induce similar damage in rhesus monkeys (Brewer et al., 1994a; Classen et al., 1999; Genovese et al., 1995, 1998; Kamchonwongpaisan et al., 1997; Li et al., 2007a; Petras et al., 1997). A similar finding was observed for rats treated with oral AL, which was reported to have similar pathological neurotoxicity following an oral dose at 160 mg/kg daily for 9 days (Si et al., 2007).

Despite extensive studies of AE, AM, and AL neurotoxicity, there is no evidence of neurotoxicity in animals related to another water soluble ART derivative, artesunate (AS), the most widely used ART in humans (Li & Wein, 2010). AS was designed for intravenous injection and, up to now, no neurotoxicity (pathologic or behavioural) has been observed in animals following intravenous administration at any repeated doses up to its maximum tolerated doses (MTD). The MTD of AS has been shown to be 240 mg/kg following intravenous injection daily in rats for 3 days, but no neurotoxicity was detected in these animals (Xie et al., 2005). In another study, intravenous AS in sodium bicarbonate dosed daily for 7 days at 120 mg/kg had no effect on neurotoxicity scores (our unpublished data). A third study of AS treatment in rats administered one intramuscular injection of AS at a high dose of 420 mg/kg did not induce any neuronal necrosis. In addition, dosing of up to 200 mg/kg of


Pharmacokinetic and Pharmacodynamic Profiles of Artemisinin Derivatives Influence Drug Neurotoxicity in Animals


This book, "Readings in Advanced Pharmacokinetics - Theory, Methods and Applications", covers up to date information and practical topics related to the study of drug pharmacokinetics in humans and in animals. The book is designed to offer scientists, clinicians and researchers a choice to logically build their knowledge in pharmacokinetics from basic concepts to advanced applications. This book is organized into two sections. The first section discusses advanced theories that include a wide range of topics; from bioequivalence studies, pharmacogenomics in relation to pharmacokinetics, computer based simulation concepts to drug interactions of herbal medicines and veterinary pharmacokinetics. The second section advances theory to practice offering several examples of methods and applications in advanced pharmacokinetics.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.