Pharmacokinetics of the Sri Lankan hump-nosed pit viper (*Hypnale hypnale*) venom following intravenous and intramuscular injections of the venom into rabbits

Choo Hock Tan, Si Mui Sim, Christine Ariaranee Gnanathasan, Shin Yee Fung, Nget Hong Tan

*Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia*

*Department of Molecular Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*

*Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Sri Lanka*

**ABSTRACT**

The knowledge of venom pharmacokinetics is essential to improve the understanding of envenomation pathophysiology. Using a double-sandwich ELISA, this study investigated the pharmacokinetics of the venom of a hump-nosed pit viper (*Hypnale hypnale*) following intravenous and intramuscular injections into rabbits. The pharmacokinetics of the venom injected intravenously fitted a three-compartment model. There is a rapid (t1/2α = 0.4 h) and a slow (t1/2β = 0.8 h) distribution phase, followed by a long elimination phase (t1/2γ = 19.3 h) with a systemic clearance of 6.8 mL h⁻¹ kg⁻¹, consistent with the prolonged abnormal hemostasis reported in *H. hypnale* envenomation. On intramuscular route, multiple peak concentrations observed in the beginning implied a more complex venom absorption and/or distribution pattern. The terminal half-life, volume of distribution by area and systemic clearance of the venom injected intramuscularly were nevertheless not significantly different (p > 0.05) from that of the venom injected intravenously. The intramuscular bioavailability was exceptionally low (Fₘₐₓ = 4%), accountable for the highly varied median lethal doses between intravenous and intramuscular envenomations in animals. The findings indicate that the intramuscular route of administration does not significantly alter the pharmacokinetics of *H. hypnale* venom although it significantly reduces the systemic bioavailability of the venom.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Snake envenomation is a neglected tropical disease and a disease of poverty (Gutiérrez et al., 2006; Harrison et al., 2009; WHO, 2010). There are approximately 5.5 million snakebite cases yearly, of these at least 4,210,000 envenomings and 20,000 deaths occur worldwide, although the figures in reality may soar as high as 1,841,000 envenomings and 94,000 deaths (Kasturiratne et al., 2008). The problem is common in developing and under-developed countries, affecting mainly agricultural workers who are usually the sole breadwinners in the families.

Optimization of snakebite management and antivenom use rely greatly on the toxicological characterization of a venom. The essential knowledge from which includes not only the venom's composition and toxic activities, but also its disposition in the body i.e. the pharmacological profile. Unfortunately, for over half a century, the management of

**ARTICLE INFO**

Article History:
Received 14 August 2013
Received in revised form 26 November 2013
Accepted 30 December 2013
Available online 9 January 2014

Keywords:
*Hypnale hypnale*
Hump-nosed pit viper
Snake envenomation
Venom pharmacokinetics
ELISA
Intramuscular bioavailability

Abbreviations: anti-HH, anti-*Hypnale hypnale* venom; AUC, area under the curve; Clₐ, systemic clearance by body weight; ELISA, enzyme-linked immunosorbent assay; h, hour; H₂SO₄, sulfuric acid; HRP, horseradish peroxidase; i.m., intramuscular; i.v., intravenous; OPD, ortho-phenylenediamine; PBS, phosphate-buffered saline; t₁/₂ₐ, half-life at distribution phase; t₁/₂β, half-life at elimination phase; Vₘₐₙ, volume of distribution by area.

*Corresponding author. Tel.: +60 3 79674851; fax: +60 3 79674811.
E-mail addresses: tanchoock@gmail.com, tanch@um.edu.my (C.H. Tan).

0041-0101/ – see front matter © 2014 Elsevier Ltd. All rights reserved.