

Pharmacokinetics of Novel Mebendazole Formulations for *Trichinella spiralis* Infection Treatment, in CBI-IGE Mice †

Ana V. Codina ^{1,2,*}, Ariana Rosales ³, Valeria Marizza ¹, Paula García ⁴, Mauro Morri ⁴, Maria Celina Lamas ^{3,5}, Lucila Hinrichsen ^{1,2}

¹ Instituto de Genética Experimental, Facultad de Ciencias Médicas, UNR

² CIC-UNR

³ Departamento de Farmacia, Facultad de Ciencias Bioquímicas y Farmacéuticas, UNR

⁴ Planta Piloto de Producción de Medicamentos, Facultad de Ciencias Bioquímicas y Farmacéuticas, UNR

⁵ IQUIR-CONICET

* Correspondence: vikicodina@hotmail.com (A.V.M.);

† Presented at The Sixth International Meeting of Pharmaceutical Sciences (RICiFa), November 10-12, 2021, Córdoba, Argentina

Received: 26.04.2022; Revised: 4.05.2022; Accepted: 6.05.2022; Published: 8.05.2022

Abstract: Mebendazole (MBZ), an anthelmintic compound widely used to treat systemic nematode infections, has low oral bioavailability and limited effectiveness due to its extremely poor water solubility. Therefore, high doses of MBZ are ordinarily used, which may cause numerous adverse effects. This research aimed to determine whether two novel MBZ formulations developed to improve the drug solubility, a nanoparticulate system (Np) and an inclusion complex with β -cyclodextrin citrate (Comp), showed enhanced bioavailability compared to pure MBZ. Adult CBI+ mice, highly susceptible to infection with *Trichinella spiralis*, were used. A single dose of each preparation (15 mg MBZ/kg bw) was administered orally to mice, and MBZ was quantified in plasma by high-performance liquid chromatography. Male and female mice given Np or Comp showed a significantly higher maximum plasmatic concentration (C_{max}) than those receiving pure MBZ (σ , $C_{max_{MBZ}}=0.3\pm 0.11$, $C_{max_{Np}}=1.5\pm 0.08$, $C_{max_{Comp}}=1.1\pm 0.04$, $P=0.0002$; ϕ , $C_{max_{MBZ}}=0.2\pm 0.02$, $C_{max_{Np}}=1.3\pm 0.09$, $C_{max_{Comp}}=1.4\pm 0.08$, σ , $P<0.0001$). In addition, the area under the curve (AUC) was higher in animals given the formulations (σ , $AUC_{MBZ}=0.7\pm 0.33$, $AUC_{Np}=9.8\pm 2.54$, $AUC_{Comp}=8.1\pm 1.13$, $P=0.0155$; ϕ , $AUC_{MBZ}=1.8\pm 0.40$, $AUC_{Np}=10.1\pm 0.62$, $AUC_{Comp}=9.0\pm 0.68$, $P=0.0057$). The pharmacokinetic analysis indicates that the formulations optimize MBZ bioavailability in both males and females. Thus, these MBZ formulations proved adequate to test their therapeutic efficacy *in vivo* and could provide the basis for establishing an effective -dose therapy for treating trichinellosis.

Keywords: Mebendazole; nanoparticles; cyclodextrin complexes; bioavailability.

© 2022 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Funding

This research was funded by SECTEI Santa Fe 2018, grant number IO-2017-00220, and SECTEI UNR 2018/2019, Res. 5601/2018.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.