Pharmacological Evaluation of Two New Isoniazid-Derived Compounds in a Mouse Model of Tuberculosis

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Introduction

Tuberculosis (TB) continues to be one of the deadliest diseases in the world. The emergence of multi-drug-resistant strains of \textit{M. tuberculosis}, the unbearable side effects of the available drugs and the frequent patient non-compliance in completing the therapy have increased the need for development of new effective agents to treat TB. Isoniazid (INH) is the most prescribed drug for active TB and prophylaxis, and requires activation by the enzyme KatG. The \textit{M. tuberculosis} enoyl-ACP reductase (InhA) has been shown to be the primary target for INH. Our group has published the rational design and synthesis of new isoniazid-derived compounds with possible anti-TB activity (Oliveira, 2006). Importantly, it was shown that these compounds do not require activation by KatG to bind its molecular target, InhA (Oliveira, 2004). We have also demonstrated that these INH analogs are able to inhibit \textit{in vitro} the activity of wild-type and INH-resistant \textit{M. tuberculosis} InhA (Vasconcelos, 2008). In addiction, these compounds were active against cultures of \textit{M. tuberculosis} H37Rv and two INH-resistant clinical isolates, showing a satisfactory efficacy \textit{in vitro} (Basso, 2010). This work describes the pre-clinical evaluation of two pentacyano(isoniazid)ferrateII complexes, named IQG-607 and IQG-639, in a mouse model of TB.

Methods

All the experimental protocols were approved by the local Animal Ethics Committee (CEUA 09/00094). Male Swiss mice were infected intravenously through the retro-orbital
sinus, with $1 \times 10^7$ viable *M. tuberculosis* bacilli suspended in 0.2 ml of Middlebrook 7H9 medium. Treatment was started 5 days post-infection, and the compounds IQG-607 and IQG-639 (250 mg/kg) were administered orally, once a day, during 28 days. Separate groups of mice were treated at the same schedules of treatment with the reference drug INH (25 mg/kg; positive control) or saline solution (negative control). At the end of treatments, mice were sacrificed by isoflurane inhalation. The spleens and lungs were aseptically removed, and the spleen weight (in grams) was determined. These organs were homogenized and the colony-forming units (CFU) were determined after 28 days of incubation in solid medium, at 37 °C.

**Results and Discussion**

*M. tuberculosis*-infected mice showed a marked enhancement of the spleen weight, when compared to the non-infected group. Either IQG-607 or INH significantly reduced *M. tuberculosis*-induced splenomegaly, with inhibition percentages of 50 and 58 %, respectively. On the other hand, IQG-639 failed to significantly affect this parameter. Moreover, CFU number was practically abolished in both spleens and lungs of IQG-607- and INH-treated groups, whereas IQG-639 was not capable of significantly modifying CFU counting. Additional experiments are being currently performed to determine the pharmacokinetic and toxicological parameters of these compounds. The promising activity of IQG-607 in *M. tuberculosis*-infected mice suggests that it is a good candidate for clinical development as a new anti-tuberculosis agent.

**References**


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