Pharmacokinetic studies of a three-component complex that repurposes the front line antibiotic isoniazid against *Mycobacterium tuberculosis*

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Introduction

The frontline tuberculosis (Tb) antibiotic isoniazid has been repurposed using a three component complex aimed at increasing the delivery efficiency and adding new avenues to its mechanism of action. This study focuses on pharmacokinetic studies of the isoniazid-sucrose copper (II)-PEG-3350 complex.

Experimental

The assays include the Plasma Protein Binding Assay (85.8%), Caco-2 Permeability Assay (B/APapp, 0.13 $x10^{-6}$ cm/s), Cytochrome P450 Inhibition Assay (i.e. CYP2B6, IC_{50} = 7.26 mM), In vitro microsomal Stability Assay ($t_{1/2}$ NADPH-Dependent > 240 min), and HepG2 Cytotoxicity (no toxicity). FT-ICR was utilized to understand the various complexes formed (i.e. Cu-$INH_1(H_2O)_x$, Cu-$(SUC)_1(H2O)_x$, Cu-$(H_2O)_x(INH)_1(SUC)_1$, etc.)

Results and Discussion

This work indicates that binding the non-reducing disaccharide sucrose to Cu(II) impacts the mechanism of action of INH. The hexavalent copper(II) was selected for its ability to bind the amines in INH and the oxygen atoms of sucrose and form a single complex (Cu-INH-SUC). Copper can induce a series of redox reactions that can produce toxic species such as the hydroxyl radical, peroxide, and superoxide. The pharmacokinetic tests done in this paper support that when compared to pure INH, the FCC has a higher toxicity range toward eukaryotic cells, increased protein binding, lower permeability, a higher half-life that extends the clearing time, and lower inhibition of cytochrome enzymes.

Conclusions

This indicates that the Four component complex has different chemical, physical and medicinal properties than pure INH. Past work measuring MIC values of the complex indicates a significantly lower dose may be possible which may allow for the drug to be administrated via an alternative technique such as weekly subcutaneous applications or an inhalation technique. Due to the low permeability found for the FCC in the CaCo2 assay, these techniques may be the most promising administration route for the INH complex.

9.4 T FT-ICR analysis of PEG-3350 (part Of spectra).

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References:

[1] Manning, T.J. et al., Tuberculosis, **107**, 149-155 (2017).