Impact of Hyaluronidase on Long-Acting Drug Release Pharmacokinetics in Murine Models

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BACKGROUND

- Developing long-acting injectable (LAI) drugs for the prevention/treatment of HIV and tuberculosis is of great interest. A key limitation in LAI development is the injection volume required to sustain active drug exposures.
- We hypothesize that the extracellular matrix-degrading enzyme hyaluronidase (HYL) may increase tolerable injection volumes of LAI drugs such as cabotegravir.
- Co-administration of HYL may improve the maximum tolerable volume of LAIs, however, HYL-induced modulation of the tissue around the LAI depot may impact drug release and therefore pharmacokinetic (PK) profiles.
- To examine this potential impact, we conducted a pilot study in mice to evaluate the effect of HYL co-administration on the release PK profile of the paradigm LAI paliperidone palmitate (PP), a long acting, slow-release prodrug of paliperidone (PAL), which has substantial preclinical and clinical PK data available publicly for comparison.

METHODS

- Adult female BALB/c mice were dosed in groups as follows:

Group	Description
1. PP	Intramuscular (IM) 62.4 mg/kg PP alone
2. PP+ Buffer	IM 62.4 mg/kg PP plus buffer (normal saline)
3. PP + 5 HYL	IM 62.4 mg/kg PP plus 5 units HYL
4. PP+ 15 HYL	IM 62.4 mg/kg PP plus 15 units HYL
5. PAL IV	Intravenous (IV) injection of 3.5 mg/kg PAL

- HYL was dissolved in normal saline. PP (Invega Sustenna formulation) was mixed with saline (+/- HYL) just prior to IM injections, which were administered in the right hind thigh muscle. PAL for IV injection was dissolved in 10 mM sodium-acetate buffer pH 4.0.
- Blood (4 mice/group/time point) was collected serially at 0.25, 1, 2, 4, 7, 10, 24, 48, 72, 96, 168, 336, and 672 h post IM injections; and at 0.6, 0.25, 0.5, 1, 2, 4, 7, 10, and 24 h post IV injection.
- PAL concentrations were measured in the plasma by a validated LC-MS assay.
- IV PK was used for deconvolution of the IM PK profiles to aid fitting of a PK model to describe the data and to determine the % bioavailability (F).

Co-administration of hyaluronidase has promise for increasing tolerable volumes of long-acting injectable drug formulations.

RESULTS

- Observed PAL plasma concentrations (mean +/- sd) are shown below in figure 1a), and PK model fittings to the data in figure 1b).
- Deconvolution of the IM PK profiles suggested 2 parallel release processes from the injection site depot, with the 2nd process incorporating a lag-time.
- Co-administration of HYL appears to increase exposure in the 1st week of the timecourse (AUC0-7d and Cmax both ~2.5x greater with HYL present) with similar effect for either 5 or 15 units HYL.

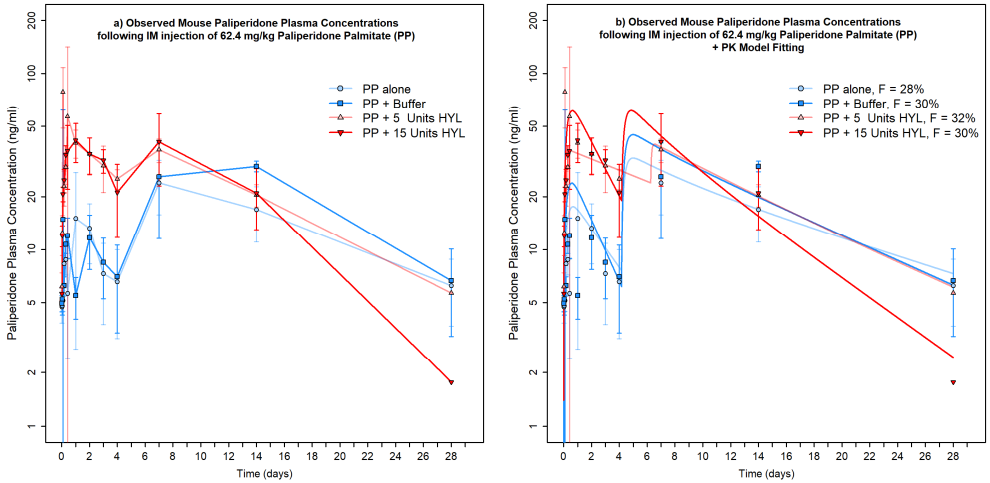

Figure 1: Plasma Concentration-Time PK Profiles for Paliperidone following IM injection of Paliperidone Palmitate

CONCLUSIONS

- Co-administration of HYL alters depot release of PAL in the 1st week (168h) following IM injection to BALB/c mice, increasing plasma exposure. Non-compartmental AUC and Cmax values were calculated as follows:

Group	AUC (ng.h/ml)		Bioavailability (F)	Cmax (ng/ml)
	0-tlast	0-168h		
1. PP	9391.3	2064.4	19.4%	23.9
2. PP + Buffer	12819.5	2036.7	26.5%	29.7
3. PP + 5 HYL	14804.0	5612.3	30.7%	78.6
4. PP + 15 HYL	14100.8	5397.1	29.2%	41.5
5. Group PAL IV	4090.8	4223.0*		

*$AUC_{0\text{-}inf}$

- HYL did not compromise the long-acting exposures from IM administration of this formulation to mice, and prolonged exposure was still maintained for 28 days.
- Higher exposures early in the profile may necessitate further evaluation of the safety and tolerability. However, these data support further investigation of HYL as an approach to increase injection volumes for anti-infective LAIs, such as cabotegravir / rilpivirine.
- Dual depot release rates suggested by the data, with potential modulation by HYL, are consistent with mechanistic descriptions of depot release processes involving resident phagocytic immune cells.
- Future work will include investigation of :
  - histopathology of depot sites +/- HYL
  - effects of increased dosing volume
  - HYL depot release effects in rats
  - lower weight normalised doses of HYL

ADDITIONAL KEY INFORMATION

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