Mechanistic modeling of intramuscular administration of long-acting injectable suspensions accounting for fibrosis at the depot site

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PURPOSE

- Antipsychotic drugs formulated as long-acting injectables (LAIs) significantly improve patient compliance compared to regimens that require daily oral administration[1]. However, the clinical development of LAIs has proven challenging due to limited understanding of the tissue response to injected particles (e.g., inflammation, fibrosis formation) impacting *in vivo* performance.
- Physiologically-based pharmacokinetic (PBPK) models could be valuable in establishing a link between *in vitro* formulation characteristics and *in vivo* performance while incorporating formulation interactions with the physiology at the injection site.
- The purpose of this study was to use PBPK modeling to delineate the *in vivo* performance of an LAI suspension, informed by *in vitro* data, and accounting for physiological responses at the injection site in humans.
- Aripiprazole (AR), formulated as prodrug AR-lauroxil (AR-L) for LAI, was used as a model drug.

METHODS

- All simulations were performed using GastroPlus® 9.8.3 (Simulations Plus, Inc). The PBPK model assumed quick AR-L to AR conversion, not impacting the rate of AR appearance in plasma[2].
- The systemic PK model was established based on AR characteristics, while dissolution at the depot site was based on AR-L properties, such as solubility.
- The physicochemical and biopharmaceutical properties of AR-L and AR were obtained from literature or public database[3,4] or predicted by ADMET Predictor® 10.3 (Simulations Plus, Inc.).
- *In vitro* formulation characterization (particle size distribution) of the drug product Aristada® was conducted as part of this project.
- AR systemic disposition and elimination was described by a three-compartment PK model that was fitted to plasma concentration-time profiles after AR oral solution administration (15, 20, and 30 mg)[5]. The model was validated with data after oral administration of AR solution (5 and 10 mg)[5] and tablet (5, 10, and 15 mg)[4].
- AR systemic disposition after intramuscular (IM) solution administration[6] was used to inform the muscle-to-plasma partition coefficient.
- This model was then utilized to simulate AR exposure after IM administration of Aristada® (AR-L suspension) at three dose levels (150, 300, and 400 mg AR equivalent)[7].
- A presumed immune cell layer (ICL) formed around the solid particles[8] was included in the model:
  - The ICL surface area (SA) was estimated from the injected dose.
  - The time-dependent change in the ICL thickness was fitted to the observed PK data for the 400 mg eq IM Aristada® dose.
  - Drug diffusion through the ICL was parameterized using AR-L logP.
- The same kinetics of ICL thickness was used in simulation of the remaining IM Aristada® doses.

RESULTS

- The developed model adequately described the observed plasma profiles of AR following oral administration in humans with all the simulated Cmax and AUC_{0-t} values within ± 25% of the observed values. The simulated Cmax and AUC_{0-t} for IM administration of AR solution were also within 25% of the observed values (Table 1).

Table 1. *Comparison of aripiprazole Cmax and AUC after oral and intramuscular administration of aripiprazole (AR).*

	Cmax (ng/mL):			AUC 0-t (ng-h/mL):		
	Observed	Simulated	S/O	Observed	Simulated	S/O
Oral Solution 15 mg	72.9	74.6	1.02	5146.1	4483.7	0.87
Oral Solution 20 mg	88.7	100.7	1.13	6626.8	6076.7	0.92
Oral Solution 30 mg	126.6	151.6	1.20	9879.3	9271.6	0.94
Oral Solution 5mg	24.0	22.7	0.95	1598.2	1356.1	0.85
Oral Solution 10 mg	46.0	48.5	1.05	3293.3	2903.2	0.88
Oral Tablet 5 mg	22.9	19.4	0.85	1664.9	1300.8	0.78
Oral Tablet 10 mg	39.6	41.0	1.04	2832.6	2786	0.98
Oral Tablet 15 mg	55.2	62.4	1.13	4306.3	4300.9	1.00
IM Solution 5 mg	20.6	23.1	1.12	1423.2	1644.5	1.16

S/O = Simulated/ Observed

Table 2. *Comparison of aripiprazole Cmax and AUC0-t after intramuscular suspension administration of aripiprazole lauroxil (AR-L). Model accounting for immune cell layer*

	Cmax (ng/mL):			AUC 0-t (ng-h/mL):		
	Observed	Simulated	S/O	Observed	Simulated	S/O
IM suspension 150 mg eq.	40.7	41.2	1.01	52810	46800	0.89
IM suspension 300 mg eq.	87.6	104.2	1.19	91910	117300	1.28
IM suspension 400 mg eq.	97.4	138.0	1.42	138100	157500	1.14

S/O = Simulated/ Observed

- The observed plasma concentration-time profiles after IM administration of AR-L suspension showed a delay in the systemic appearance of AR, which was attributed to the formation of a dynamic ICL around the injected material. The model without the inclusion of ICL predicted an earlier Tmax than observed (Figure 1).
- The ICL presents an additional barrier for the dissolved drug to diffuse through before reaching the systemic circulation, explaining the observed delayed Tmax. The inclusion of an ICL in the model resulted in adequate predictions (prediction errors less than 50%) of the exposure parameters (Table 2) and of the shape of the plasma concentration-time profiles (Figure 2) for all three dose levels.

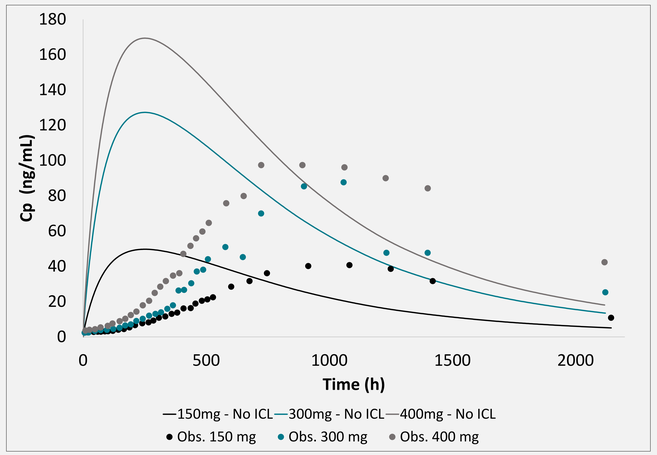

Figure 1. Observed (symbols) and predicted (lines) AR plasma concentration vs time profile after IM administration of aripiprazole lauroxil (AR-L) suspension in humans. Model without the inclusion of Immune cell layer.

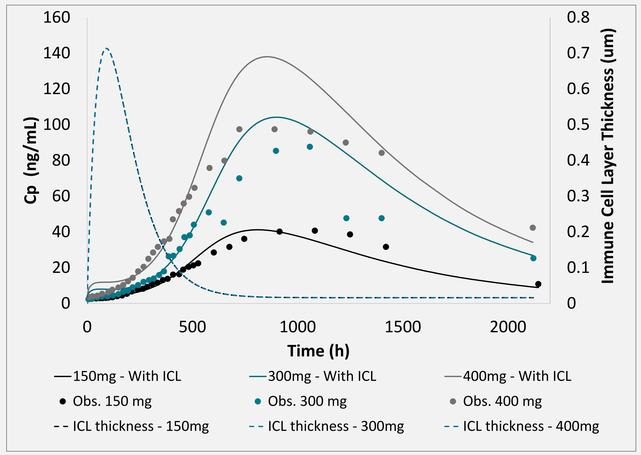

Figure 2. Observed (symbols) and predicted (solid lines) AR plasma concentration vs time profile after IM administration of aripiprazole lauroxil (AR-L) suspension in humans. Model accounting for immune cell layer. Dashed lines represent the time-dependent change in the immune cell layer thickness (superimposable between doses).

CONCLUSIONS

- The drug absorption and PK profile of LAI suspensions are primarily affected by the kinetics of drug dissolution and the local inflammatory response at the injection site.
- The inflammatory response to the injected solid materials may result in formation of a fibrous band that traps the drug crystals at the injection site, resulting in delayed drug release and absorption.
- Utilizing SA calculation based on solid material and the same time-dependent change in ICL thickness across all dose levels resulted in reasonable predictions of AR PK profiles following IM administration of multiple strengths of the AR-L suspension.
- This shows the utility of PBPK model in mechanistically describing the in vivo performance of LAIs.
- Predicting the exposure of LAIs is challenging given the high variability and lack of available data to accurately parametrize the model, hence further studies are needed to validate and refine this approach.

FUNDING, DISCLAIMER AND REFERENCES

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