M1030-13-86

The Effect of the Local Tissue Response on the Pharmacokinetics of Long-Acting Injectable Formulations

Azar Shahraz[1], James Mullin[2], Viera Lukacova[2]

[1]Simulations Plus, Inc. (current affiliation: Alnylam® Pharmaceuticals)

[2]Simulations Plus, Inc. 42505 10th Street West, Lancaster, California 93534, USA

CONTACT INFORMATION: viera@simulations-plus.com

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PURPOSE

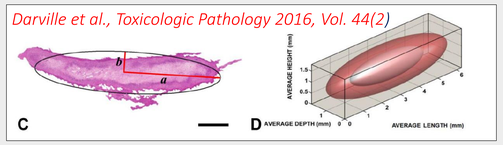
Modeling consequences of localized chronic inflammation in tissue on drug diffusion and exposure caused by prolonged therapy with long-acting formulations.

OBJECTIVE(S)

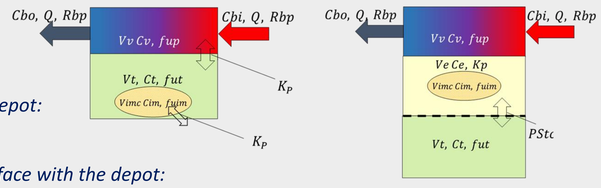
Recently, long-acting injectable (LAI) drug formulations have attracted much attention for prolonged drug exposure from weeks to several months. However, the administration of foreign materials in the tissue can result in a variety of injection site reactions (ISRs), which have not been well characterized in the literature[1,2]. The focus of the present work is to model consequences of localized chronic inflammation in tissue on drug diffusion and exposure caused by prolonged therapy with long-acting formulations.

METHOD(S)

In this study, the tissue response triggered by the parenteral injection is modeled as an inflammatory rim surrounded the formulation depot, which can serve as a physical barrier for diffusion of drugs as well as acidic degradation products, increasing auto-catalyzed PLGA hydrolysis and also preventing drug diffusion away from the microparticles. We characterized the dynamics of this immune cell layer (ICL) mainly based on the in vivo study performed by Darville et al.[2] to determine the local histopathological and immunological alterations generated by the IM injection of PP-LAI and polystyrene (PS) nano-/microsuspensions in the rat.

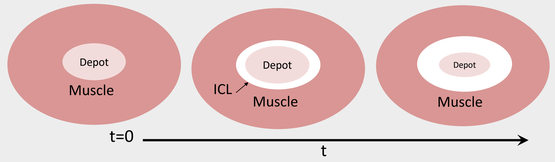


To account for the slow diffusion of the API through the ICL, the layer is divided to five (5) sublayers. The first sublayer is in the direct contact with the formulation depot and the last sublayer with the tissue compartment in the perfusion-limited tissue model or extracellular compartment in the permeability-limited tissue model. The model accounts for the API diffusion through ICL with a time-varying thickness and a nonspecific tissue binding.

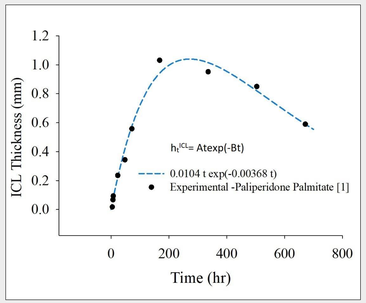


- *ICL* unbound *concentration:* $C_{1,u}^{ICL} = C^{Dep}$
- *ICL total concentration at the interface with Depot:* $C_{1,t}^{ICL} = K_p^{ICL/Dep}\, C^{Dep}$
- *Mass balance equation for API in ICL at interface with the depot:* $\left(\frac{V^{Dep}}{K_p^{ICL/Dep}} + V_1^{ICL}\right)\frac{dC_{1,t}^{ICL}}{dt} = -\frac{Diff}{h_1^{ICL}} \times SA \times \left(C_{2,u}^{ICL} - C_{1,u}^{ICL}\right)$
- *API diffusion through the ICL :* $\frac{dC_{j,t}^{ICL}}{dt} = \frac{Diff}{\left(h_j^{ICL}\right)^2} \times \left(C_{j-1,u}^{ICL} - 2C_{j,u}^{ICL} + C_{j+1,u}^{ICL}\right)$
- *The mass balance in the last sublayer (j=5) which is in contact with tissue or extracellular compartment can be written as (X= tissue or extracellular):* $\left(V^x K_p^{x/ICL} + V_5^{ICL}\right)\frac{dC_{5,t}^{ICL}}{dt} = -\frac{Diff}{h_5^{ICL}} \times SA \times \left(C_{5,u}^{ICL} - C_{4,u}^{ICL}\right)$
- *The thickness of the ICL layer at any time :* $h_t^{ICL} = \sum_{j=1}^{5} h_j^{ICL} = Ate^{xp}(-Bt)$

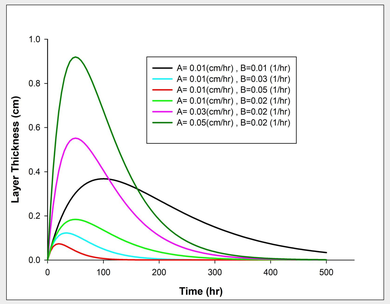
RESULT(S)



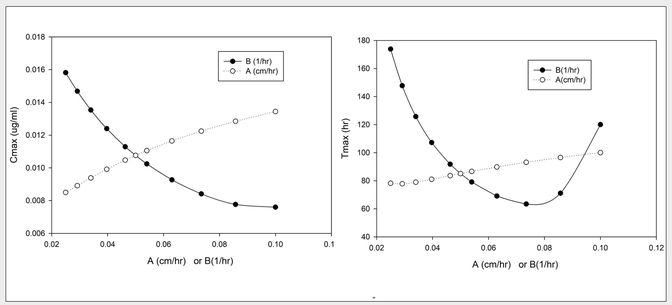
Schematic representation of the dynamic courses of cellular infiltration within the depot



The effect of parameter A and B on the dynamics of the immune cell layer.



The dynamics of infiltrated cell layer after a single intramuscular administration of paliperidone palmitate long-acting injectable in the rat



The effect of thickness parameters on Cmax and Tmax after single intramuscular administration of paliperidone palmitate long-acting injectable in the rat.

CONCLUSION(S)

Tissue response following administration of LAIs was modeled by an immune cell mediated diffusion barrier.

- Using the mathematical model obtained from rat data, parameter sensitivity analysis (PSA) was performed on both thickness model parameters to study their effect on systemic exposure of human subjects after receiving single paliperidone palmitate 50 mg eq. injection in the gluteal muscle.
- We showed that Cmax increases by increasing the pre-exponential ICL growth term A(cm/hr), while it is decreasing by exponential ICL growth term, B (1/hr).
- Assuming the presence of ICL, Tmax is monotonically increasing when pre-exponential ICL growth term is increasing, however the effect of exponential ICL growth term on the Tmax is not monotonic.
- No effect on AUC was observed during the PSA analysis.

FUNDING / REFERENCE

The work was done under funding from the FDA (grant 1U01FD005463-02)

[1] Darville N, et al., Toxicologic Pathology 2016, Vol. 44(2)

[2] Doty A C, Doctoral Dissertation, University of Michigan 2015

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