Poster 518

Optimisation of Intramuscular Sustained Release-Nano-Formulations Using In Silico Modelling

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Overview

- Antiretrovirals (ARVs) can find clinical application not only in the treatment of HIV infection but also in its prevention. Recently pre-exposure prophylaxis (PrEP) strategies have been developed for subjects who are at high risk of acquiring the infection [1].
- Currently available oral formulations necessitate lifelong, daily dosing and a suboptimal adherence, places the patient at risk of treatment failure and low rates of protection for PrEP [2].
- The introduction of injectable sustained-release nano-formulations (NFs) could represent a pharmacological option opening the possibility to simplify dosing regimens, increase adherence, reduce the amount of drug consumed and thus decrease the overall cost of the treatment and PrEP [3].
- Physiologically based pharmacokinetic (PBPK) modelling is the mathematical description of anatomical, physiological and molecular processes defining drug distribution (Figure 1b), through the integration of drug characteristics and patient-specific factors (Figure 1a) [18].
- The aim of this study was to simulate the PK of intramuscular (IM) sustained release NFs using PBPK modelling. Existing ARVs available as oral formulations were assessed for compatibility. Theoretical target dose and release rate combinations for once weekly and once monthly formats were identified.

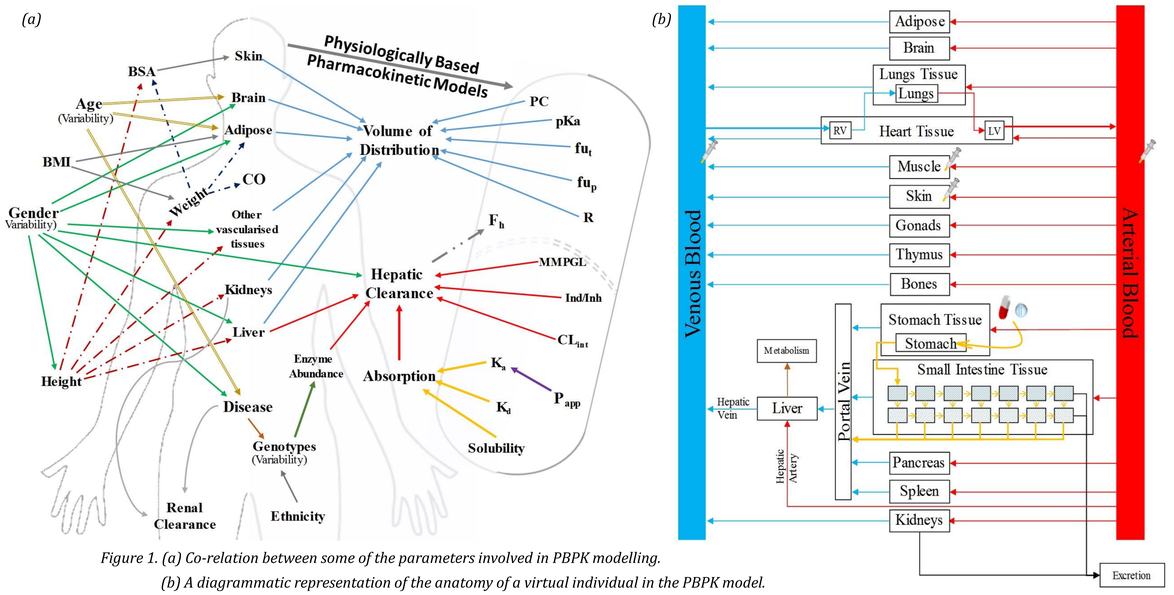

Figure 1. (a) Co-relation between some of the parameters involved in PBPK modelling. (b) A diagrammatic representation of the anatomy of a virtual individual in the PBPK model.

Methods

- Virtual patients were generated using a population physiology model [4]. Age, BMI and weight were used to allometrically scale organ weights and cardiac output [4]. A virtual population of healthy Caucasian individuals with a mean age of 39 years, (range 18-60) was generated.
- Validated equations were used for the calculation of volume of distribution and processes regulating absorption, distribution and elimination [5-9].
- Physicochemical properties, *in vitro* apparent permeability, *in vitro* intrinsic clearance and cytochrome P450 induction were obtained from the literature.
- PK of ARVs was predicted using Simbiology (in MATLAB, version 2013b).
- Simulations for oral PK were first developed to validate the PBPK models against available clinical data. The PBPK model for rilpivirine (RPV) was then validated against the published PK of long-acting RPV to legitimise the approach. Finally, the PK for IM administration of all the ARVs at various dose and release rate combinations was simulated.
- For the first validation, oral absorption was simulated using a compartmental absorption and transit model [6]. For IM depot simulations, a discrete compartment was introduced to represent muscle tissue containing the depot, and release of drug from the depot into the blood plasma was assumed to follow dose-dependent first-order kinetics.
- Dose and release rate combinations of the 8 ARVs were optimised to give predicted median plasma concentrations above the protein binding corrected IC_{95} ($PBIC_{95}$) or IC_{95} values 7- or 30-days after administration.

Results

- The simulated PK parameters for oral administration were in agreement with previously published clinical data (data not shown).
- Validation of the PBPK model was subsequently conducted against an existing long-acting IM formulation of RPV (600 mg; 100 mg mL^{-1}) [10]. The mean values for AUC were 84.0 ng mL^{-1} h vs. 83.38 ± 33.34 ng mL^{-1} h, C_{max} 96.7 ng mL^{-1} vs. 86.73 ± 30.51 ng mL^{-1} and C_{trough} 15.7 vs. 11.81 ± 6.3 ng mL^{-1} for clinical versus predicted data with a predicted release rate of 0.0011 ± 0.0001 h^{-1} for the clinical IM formulation (Figure 2).
- A summary of the predicted values for AUC, C_{max} and C_{min} for 8 ARVs along with dose and release rate combinations predicted to be optimal is shown in Table 1.
- Dolutegravir, efavirenz, emtricitabine, raltegravir, tenofovir and RPV were predicted to be the suitable candidates for monthly IM injection as shown in Figure 3.

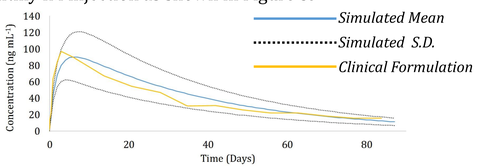

Figure 2. Validation of the PBPK strategy against clinical data for an existing RPV sustained-release formulation (600 mg; 100 mg mL^{-1}).

Table 1: Summary of Dose, Release Rate, Frequency of Administration and Pharmacokinetics of Solid Drug Nanoparticles Containing Antiretrovirals Administered Intramuscularly

Drug	IM Dose (mg)	Release Rate (h^{-1})	Frequency of Administration	AUC (μg h mL^{-1}) (Mean ± SD)	C_{max} (ng mL^{-1}) (Mean ± SD)	C_{trough} (ng mL^{-1}) (Mean ± SD)	Cut-off Limit (ng mL^{-1})
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)							
Emtricitabine	600	0.0015	**Monthly**	21.0 ± 10.9	45.8 ± 22.7	17.3 ± 10.7	14 (IC_{95}) [11]
	125	0.01	Weekly	7.2 ± 10.7	68.2 ± 79.4	14.5 ± 9.0	
Tenofovir	1500	0.001	**Monthly**	25.5 ± 17.8	56.6 ± 38.9	20.0 ± 14.0	18 (IC_{95}) [12]
	350	0.008	Weekly	6.7 ± 5.3	67.2 ± 49.1	18.7 ±13.8	
Non-Nucleoside Reverse Transcriptase Inhibitors (NRTIs)							
Efavirenz	1000	0.002	**Monthly**	190.6 ± 101.3	377.5 ± 165.6	154.0 ± 130.8	126 ($PBIC_{95}$) [5]
	200	0.015	Weekly	34.0 ± 9.1	268.5 ± 60.9	138.1 ± 81.3	
Etravirine	225	0.011	Weekly	11.7 ± 1.8	88.6 ± 12.7	59.8 ± 16.0	52 (MEC) [13]
Rilpivirine*	250	0.002	**Monthly**	40.2 ± 19.7	76.9 ± 33.6	35.0 ± 20.0	20.3 ($PBIC_{95}$) [14]
	60	0.02	Weekly	8.0 ± 2.5	71.8 ± 16.4	20.7 ± 14.0	
Integrase Inhibitors (IIs)							
Dolutegravir	105	0.002	**Monthly**	91.2 ± 9.4	192.3 ± 16.6	64.3 ± 8.1	64 ($PBIC_{95}$) [19, 15, 16]
	20	0.006	Weekly	12.3 ± 1.3	89.6 ± 9.5	65.5 ± 7.6	
Raltegravir	1000	0.002	**Monthly**	89.1 ± 17.9	62.8 ± 9.7	15.4 ± 2.5	15 ($PBIC_{95}$) [17]
	225	0.007	Weekly	17.8 ± 3.4	46.8 ± 7.2	15.8 ± 2.5	
Protease Inhibitors (PIs)							
Atazanavir	600	0.009	Weekly	124.5 ± 4.1	192.1 ± 10.7	60.6 ± 2.3	60 ($PBIC_{95}$) [17]

* Note that this dose does not apply to the existing RPV formulation. Rather, as for other listed drugs, the data represent a prediction for optimal performance of a reformulation.

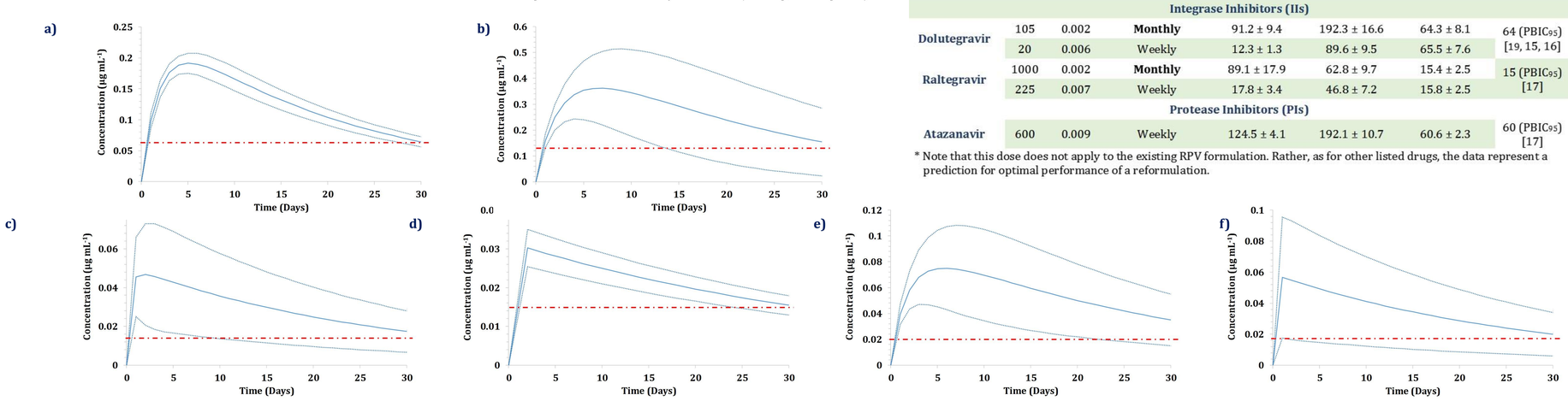

Figure 3. Simulated PK of IM sustained release NFs using PBPK modelling (a) Dolutegravir (b) Efavirenz (c) Emtricitabine (d) Raltegravir (e) RPV (f) Tenofovir. Mean Mean ± S.D. $PBIC_{95}/IC_{95}$

Conclusion

- These data are theoretical and currently there is no evidence to confirm or refute that these dose / release rate combinations can be achieved by available technologies.
- Candidate ARVs with potential for reformulation into IM depot were identified, providing the technological complexities associated with reformulation can be overcome for these agents.
- Based on known clearance of RPV, monthly exposure from 250 mg (2.5 mL equivalent for latest existing formulation) is theoretically achievable if release rate can be tuned to 0.002 h^{-1}.
- PBPK modelling may be a useful tool for defining product characteristics for sustained-release NF development.

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