Development of a PBPK model for topical lidocaine in order to predict systemic absorption in healthy volunteers, geriatrics and paediatrics

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Background

Lidocaine is a local anaesthetic available in different dermal formulations of patch, cream and gel and is widely applied in management of pain in paediatrics and adults. Systemic exposure of lidocaine presents a large difference between two studies of the same dose of the patch under same brand name [1,2].

Physiologically based pharmacokinetics models (PBPK) have a unique advantage in integrating both the drug and formulation characteristics and the underlying skin physiology to predict pharmacokinetic differences between formulations and populations. The aim of this study was to predict plasma concentration-time profile of lidocaine after topical application of lidocaine patch in different healthy volunteers, paediatrics and geriatrics and understand the formulation differences of the patch product.

Methods

A PBPK model was developed for lidocaine in Simcyp v17 using Multi-Phase and Multi-Layer (MPML) MechDermA model to predict the pharmacokinetics of lidocaine for Lidoderm [1,2] in healthy volunteers, lidocaine 5% patch in geriatrics [3] and EMLA cream in pediatrics [4]. Simulations were designed to mimic the clinical study, as closely as possible. Formulation characteristics of patch and cream were extracted form the literature and are presented in table 1. For patch, *in vitro* and *in vivo* permeation rates for Lidoderm (Endo pharmaceuticals) patch have reported [1, 2]. The slope of these profiles after correction for surface area of patch was used as release rate. Predicted and observed C_{max}, t_{max}, AUC and plasma concentration-time profiles were compared.

Table 1. Formulation parameter in Simcyp v17

Parameter	Value
Formulation pH	9 [6]
Fraction non-ionised at skin surface	97% [7]
Diameter of dispersed phase droplets (um)	0.2 [8]
Diameter of particles (um)	35 [9]
Diffusion coefficient (cm2/h)	0.033 [7]
Drug solubility ratio dispersed/continuous phase	257.04 (estimate from 10^{logp})
Droplet permeability	0.446
Drug solubility in continuous phases (mg/ml)	0.72 [10]

The difference between observed exposure (3.1 fold) after Lidoderm patch [1,2] was applied to release *in vitro* release rate to predict PK data.

Results

The release rate from *in vitro* and *in vivo* permeation data for three Lidoderm patches (420 cm^2) is reported as 8.6 and 4.75 mg/h, respectively [1,2]. Figure 1 shows the predicted *vs.* observed plasma concentration-time profile of Lidoderm in both studies using *in vitro* rate as input to the model. The *in vivo* based release rate reported in ref [1] of 4.75 mg/h under-predicts both profiles. The corrected *in vitro* rate for exposure differences (3 fold difference in AUC_{0-24}) between two studies (potentially due to formulation/release rate) recovered PK data well (Figure 1c).

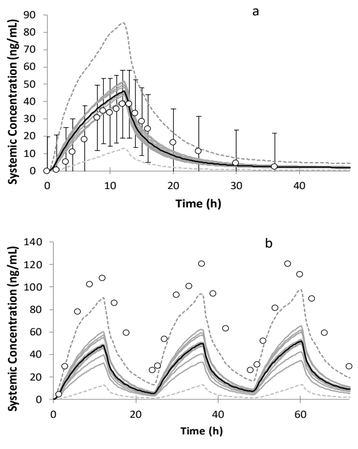

Figure 1. Plasma concentration time profile of Lidoderm from [2] (a) and from [1] (b and c). The grey lines are trials prediction, black line is the mean profile ad dotted lines are the 5th and 95th percentile of rediction. Open circles are the observed data.

In geriatrics, to achieve the same exposure as in Figure 1c, 4 patches of Lidoderm are required that indicates age-related differences between heathy and geriatric volunteers. The predicted *vs.* observed plasma profile in geriatrics using *in vitro* release rate (figure 2a) and after applying the correction factor of AUC difference (figure2b).

Figure 2. Plasma concentration time profile of Lidoderm [4] using *in vitro* release rate (a) and corrected *in vitro* release rate (b). The grey lines are trials prediction, black line is the mean profile and dotted lines are the 5th and 95th percentile of prediction. Open circles are the observed data.

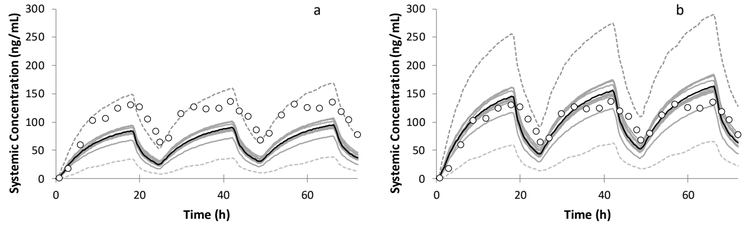

Figure 3 shows the predicted *vs.* observed plasma concentration time profile of EMLA cream in paediatrics 2-3 and 6-8 years old, respectively. For EMLA cream in healthy adults, predicted *vs.* observed C_{max} and t_{max} values reported are 0.09 *vs.* 0.12 µg/ml and 3.4 vs. 4 h, respectively.

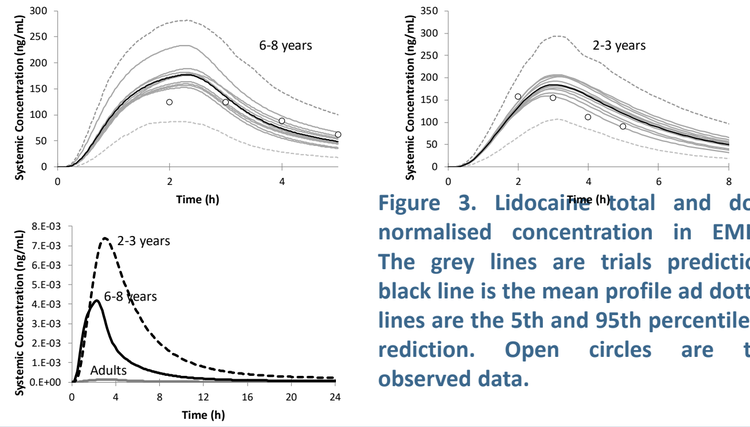

Figure 3. Lidocaine total and dose normalised concentration in EMLA. The grey lines are trials prediction, black line is the mean profile ad dotted lines are the 5th and 95th percentile of rediction. Open circles are the observed data.

Conclusions

- MPML-MechDermA model can predict transdermal absorption through skin layers and into systemic circulation reasonably well for different lidocaine formulation in different age groups.
- The difference in systemic exposure between patch studies indicate that the release rate has changed for this patch but there is no evidence in the literature.
- There are age related difference between adult and geriatrics and paediatrics and adults dermal absorption
- Further verification of this model using various compound types, age groups and formulations is required.

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