Dual Incorporation of the *in vitro* Data (IC$_{50}$) and *in vivo* (C$_{max}$) Data for the Prediction of Area Under the Curve (AUC) for Statins using Regression Models Developed for Either Pravastatin or Simvastatin

**Abstract**

Linear regression models utilizing a single time point (C$_{max}$) has been reported for pravastatin and simvastatin. A new model was developed for the prediction of AUC of statins that utilized the slopes of the above 2 models, with pharmacokinetic (C$_{max}$) and a pharmacodynamic (IC$_{50}$) value components for the statins. The prediction of AUCs for various statins (pravastatin, atorvastatin, simvastatin and rosuvastatin) was carried out using the newly developed dual pharmacokinetic and pharmacodynamic model. Generally, the AUC predictions were contained within 0.5 to 2-fold difference of the observed AUC suggesting utility of the new models. The root mean square error predictions were < 45% for the 2 models. On the basis of the present work, it is feasible to utilize both pharmacokinetic (C$_{max}$) and pharmacodynamic (IC$_{50}$) data for effectively predicting the AUC for statins. Such a new concept as described in the work may have utility in both drug discovery and development stages.

**Introduction**

Statins are reversible inhibitors of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase which is a microsomal enzyme responsible for the conversion of HMG CoA to mevalonate [1]. The recent report by Srinivas (2015) has explored the utility of a single time point strategy for predicting area under the curve (AUC) for pravastatin and simvastatin using linear regression models [2]. The applicability of such an approach was also demonstrated to other statins such as atorvastatin, lovastatin and rosuvastatin in a limited manner [1]. In the present work the utility of both pravastatin and simvastatin linear regression models to predict the AUC of other statins was explored. Since statins differ in the in vitro potency with regard to the inhibition of HMG CoA reductase, it was necessary to use the in vitro potency as a surrogate along with the respective in vivo C$_{max}$ data of the statin for prediction purposes. This report describes the dual incorporation of pharmacokinetic (C$_{max}$) and pharmacodynamic (IC$_{50}$) that has enabled the prediction of AUCs for various statins.

**Methods**

The slope values of the linear regression models for pravastatin (2.4779) and simvastatin (3.6777) were obtained from the previously published report [2]. The IC$_{50}$ values for the inhibition of HMG CoA for pravastatin (44.1 nM), simvastatin (11.2 nM), atorvastatin (8.2 nM) and rosuvastatin (5.4 nM) were obtained from the published literature [3, 4]. The C$_{max}$ and AUC$_{inf}$ values for the various statins used in the analysis were obtained from the reported pharmacokinetic studies [5–27].

**Model development and Predictions using pravastatin and simvastatin slope values**

The linear regression model was described by the following relationship that incorporated both pharmacokinetic (C$_{max}$) and pharmacodynamic (IC$_{50}$) data for prediction purposes. Using pravastatin linear regression slope:

$$\text{AUC} = 2.4779 \times C_{max} \times \frac{IC_{50} \text{ (pravastatin)}}{IC_{50} \text{ (statin : A)}}$$

Using simvastatin linear regression slope:

$$\text{AUC} = 3.6777 \times C_{max} \times \frac{IC_{50} \text{ (simvastatin)}}{IC_{50} \text{ (statin : A)}}$$

The predictions of the AUC values with the respective models were carried out on a spread-
sheet using Microsoft Excel 2010 (Microsoft Company, Seattle, USA).

Fold computation, prediction criteria and statistics
The quotient of observed AUC and predicted AUC value was used to define the fold change of the AUC prediction. The observed vs. predicted AUC values arising from the 2 models (pravastatin or simvastatin) was further evaluated separately by employing a paired t-test (double sided) using the T-test calculator (Graphpad software Inc., California, USA).

The mean absolute error (MAE) was defined as the mean of the observed AUC values minus the predicted AUC values and was computed for both the models:

\[
MAE = \frac{1}{N} \sum_{i=1}^{N} |y_i - \hat{y}_i|
\]

Mean square error (MSE) and root means square error (RMSE) in prediction for both models were performed using Microsoft Excel 2010.

\[
MSE = \frac{1}{N} \sum_{i=1}^{N} (y_i - \hat{y}_i)^2
\]

\[
RMSE = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (y_i - \hat{y}_i)^2}
\]

Results
The AUC predictions rendered by using pravastatin and simvastatin based models are illustrated in Fig. 1, 2, respectively. The

![Fig. 1 Plots showing correlation of observed vs. predicted AUC values for various statins using the PKPD model developed for pravastatin and simvastatin.](image)
predicted values for simvastatin, pravastatin, atorvastatin and rosuvastatin appeared to be comparable based on the visual inspection of the data (Fig. 1,2). Examination of the AUC fold difference suggested that generally the AUC predictions were contained within 0.5 to 2-fold difference using either of the 2 models (Fig. 1,2).

The MAE and RMSE expressed as percentage (%) were 2.42 and 42.76, respectively, for the pravastatin based model and the corresponding values were 24.99 and 44.62, respectively, for the simvastatin based model (Table 1). Fig. 3 showed excellent correlations of predicted vs. observed AUC values for various statins regardless of the type of PKPD model employed.

**Table 1** Summary statistics for the prediction of AUC values of various statins using the pharmacokinetic-pharmacodynamic model developed for pravastatin and simvastatin.

<table>
<thead>
<tr>
<th>Model type, (N size)</th>
<th>AUC of statins</th>
<th>Mean absolute error (%)</th>
<th>Root mean square error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin1 (24)</td>
<td>Observed 92.23 Predicted 90.00</td>
<td>2.23 (2.42)</td>
<td>39.44 (42.76)</td>
</tr>
<tr>
<td>Simvastatin2 (36)</td>
<td>Observed 108.60 Predicted 81.46</td>
<td>27.14 (24.99)</td>
<td>48.46 (44.62)</td>
</tr>
</tbody>
</table>

1 statins included in the analysis were simvastatin, atorvastatin, rosuvastatin
2 statins included in the analysis were pravastatin, atorvastatin, rosuvastatin
3 observed values were obtained from the published pharmacokinetic studies (ref: [5–27])

**Discussion**

In the clinic, a threshold efficacy was achieved for all the statins with differing starting dose sizes. However, the statins that have higher in vitro potency (i.e., atorvastatin and rosuvastatin) tended to show further improvement in the efficacy as the respective dose was increased. Therefore, it was postulated that incorporation of a measure of efficacy (i.e., in vitro potency data for HMG CoA reductase inhibition; IC50 value) along with the respective pharmacokinetic data (i.e., Cmax) may have utility for the AUC prediction of the statins. Because there was a report of linear regression models developed for both pravastatin and simvastatin, it easily facilitated evaluation of other statins by merely incorporation of Cmax, data of the chosen statin along with the corresponding IC50 value. In the development of the dual PKPD linear regression model, the square root transformation of the IC50 values was found appropriate to give reliable AUC values for the various statins when incorporated in the model. The untransformed “as is” IC50 values generally tended to exhibit higher predictive errors for the various statins and similarly log transformed values appeared to show higher level of deviations (data not shown).

Recently, van de Steeg et al (2013) showed the utility of combining the pharmacokinetic data with the pharmacodynamic data (efficacy data) of the various approved statins in a murine model to enable the translatability of the preclinical model to render

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**Fig. 3** A plot showing the spread of observed vs predicted AUC values for pravastatin, atorvastatin and rosuvastatin with the corresponding observed/predicted AUC fold difference. The pravastatin model was used in the analysis. The simvastatin model was used in the analysis [Closed diamonds and closed squares represent the observed and predicted values, respectively; and the open diamonds represent the ratio of the observed AUC/predicted AUC].
human predictions [28]. This work showed that incorporation of the effective liver uptake data for the various statins was necessary to improve the translatability of the efficacy in the murine model. To the best of the author’s knowledge, hitherto, the dual incorporation of pharmacokinetic and pharmacodynamic data has not been reported in a linear regression model. Since the 4 statins evaluated in this report showed differences in their IC₅₀ value for the inhibition of HMG CoA enzyme, it was thought that incorporation of the IC₅₀ value along with Cmax for each paired statin in relation to the linear regression model developed for pravastatin or simvastatin may render prediction of the AUC of the statin being evaluated. The concept was developed with the view that the intrinsic nature of this class of compounds (i.e., statins) to inhibit HMG CoA enzyme was well established and it was thought that potency of inhibition of the respective statins may be correlated with the appropriate in vivo PK parameter such as Cmax. The data from the present analysis supported such interesting novel concepts. Although RMSE values appear to be on the higher side regardless of pharmacokinetic (i.e., Cmax) and pharmacodynamic (i.e., IC₅₀) values may be possible if the focus was on a single statin render- ergenous but also were from different clinical studies rather than clinical data for AUC prediction purposes. The developed dual pharmacokinetic-pharmacodynamic model with an anchored reference drug would be based on preclinical rather than clinical data for AUC prediction purposes.

Conflict of Interest

The author has stated that he has no conflicts of interest to declare in the contents of this manuscript.

References