Modeling the Pharmacokinetics and Pharmacodynamics of a Unique Oral Hypoglycemic Agent Using Neural Networks

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Purpose. To develop a predictive population pharmacokinetic/pharmacodynamic (PK/PD) model for repaglinide (REP), an oral hypoglycemic agent, using artificial neural networks (ANNs).
Methods. REP, glucose concentrations, and demographic data from a dose ranging Phase 2 trial were divided into a training set (70%) and a test set (30%). NeuroShell Predictor™ was used to create predictive PK and PK/PD models using population covariates; evaluate the relative significance of different covariates; and simulate the effect of covariates on the PK/PD of REP. Predictive performance was evaluated by calculating root mean square error and mean error for the training and test sets. These values were compared to naive averaging (NA) and randomly generated numbers (RN).
Results. Covariates found to have an influence on PK of REP include dose, gender, race, age, and weight. Covariates affecting the glucose response included dose, gender, and weight. These differences are not expected to be clinically significant.
Conclusions. We came to the following three conclusions: 1) ANNs are more precise than NA and RN for both PK and PD; 2) the bias was acceptable for ANNs as compared with NA and RN; and 3) neural networks offer a quick and simple method for predicting, for identifying significant covariates, and for generating hypotheses.

KEY WORDS: repaglinide; neural networks; pharmacokinetics-pharmacodynamics; models; type 2 diabetes.

INTRODUCTION

Since the re-introduction of artificial neural networks (ANNs) in the late 1980s, these empirical pattern-recognition and mapping tools have been applied to complex multifactorial problems in many scientific disciplines (1). In the pharmaceutical sciences, these tools have been evaluated for formulation design and optimization (2–5), interspecies scaling (6), *in vitro–in vivo* correlation (7, 8), population pharmacokinetic (PK) analysis (9, 10), pharmacokinetic–pharmacodynamic (PK-PD) modeling, and quantitative structure–activity relationships (11–14). In general, the pattern-recognition or mapping capabilities of the ANN tools appear to be on par with traditional statistical tools. The major advantages of ANNs over traditional statistical tools include their parallel, highly nonlinear, and non-parametric mapping capabilities. However, the empirical nature of ANN mappings tends to discourage their utility because the underlying mechanistic relationships are not apparent or are difficult to decipher. One approach for defining the underlying relationships in an ANN mapping is to use a trained ANN as a simulation tool.

The objectives of this study were to investigate the utility of ANNs for recognizing relationships between subject demographic variables, PK parameters, and PD response to the drug repaglinide (Prandin®, Novo Nordisk, Princeton, New Jersey). This drug was selected for these investigations because our attempts at developing traditional population PK and PD models were not successful due (in part) to large intersubject variability. Information for appropriate dosing, which was included in the drug label (package insert), was derived via subgroup analysis of several clinical studies. The results of ANN mapping and simulations are compared with the results of the subgroup analysis.

Repaglinide is a unique oral insulin secretogogue, unrelated to the sulfonylureas, which was approved for the treatment of type-2 diabetes mellitus in 1998. Repaglinide (REP) differs from other insulin secretogogues, i.e., sulfonylureas, by chemical structure, binding site, and pharmacokinetics. The activity of REP is dependent on functioning β-cells in the pancreatic islets. It stimulates insulin release by binding to ATP-dependent K^+ channels in the β-cell membrane, sites that are distinguishable from those of sulfonylureas. Potassium channel blockade results in β-cell membrane depolarization, subsequent Ca^{2+} channel opening, Ca^{2+} influx, and induction of insulin secretion.

After oral administration, REP is rapidly absorbed from the gastrointestinal (GI) tract. Maximum plasma concentrations are reached at approximately 1 h post-dosing in healthy volunteers, as well as in diabetic patients. REP has an absolute bioavailability of about 56%. It is metabolized by oxidative biotransformation (cytochrome P-450 enzyme system) and direct glucuronidation to inactive metabolites. REP is rapidly cleared from the body, with a terminal half-life of about 1 h. The chemical structure of REP is shown in Figure 1.

METHODS

Population PK–PD analysis was performed on data generated by a Phase II, placebo-controlled, parallel design, dose-ranging study in patients with type-2 diabetes. A total of 145 patients were randomized to one of six treatment groups: placebo, repaglinide 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 4.0 mg. Each patient was dosed three times daily 15 min after a standardized meal for 4 weeks. Samples for the determination of blood glucose and REP plasma levels were collected over 24 h on Days 0, 7, 14, and 28. Non-compartmental PK analysis was used to calculate REP as well as glucose area under the curve (AUCs). Data from the above study were randomly partitioned into a training set (70%) and a test set (30%). A predictive PK model using neural network analysis (Neuroshell Predictor™, Ward Systems Group, Frederick, MD) was created using gender, age, weight, dose, and week of treatment as inputs (covariates or independent variables) and

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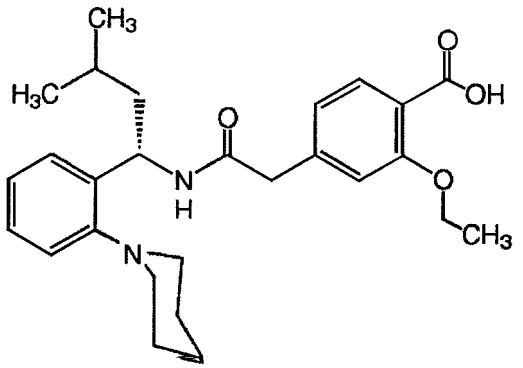

Fig. 1. Chemical structure of repaglinide.

REP AUC as output (dependent variable). The model was then used to predict REP AUC using covariates from the test data set, which was naive to the model. Predictive performance was evaluated by calculating the root mean square error (RMSE), a measure of precision, and the mean error (ME), a measure of bias (15).

Similarly, a predictive PK–PD model was created using the same covariates as the PK model, except that REP AUC was included as an additional covariate, and glucose AUC (PD measurement) was used as the output or dependent variable. Again, predictive performance was evaluated by calculating the RMSE and ME for the training and test data sets. Predictive performance was further evaluated by comparing RMSE and ME of the neural network PK and PK–PD models to those obtained by naive averaging (NA) of the data and values generated randomly (RN) within the dependent variable range, using Microsoft® Excel, version 5.

Using simulations, the predictive PK and PK–PD models obtained through neural network analysis were used to explore the effect of various patient demographics (weight, age, and gender) on the PK–PD of REP. For example, keeping all covariates constant, REP AUC was predicted for male and female patients as age and weight were varied over a range represented by the data. This was done for the lowest and highest dose of REP. Furthermore, a dose–response curve was created for both male and female patients.

Finally, the genetic algorithm component of NeuroShell Predictor™ was used to evaluate the relative significance of the covariates (or inputs) on the PK and PD of REP.

RESULTS

Figure 2, a and b, is a graphical representation of the dependent variables, repaglinide AUC, and percent change from baseline glucose AUC, respectively, across all subjects in the test data set. The plots connect observed and predicted values, providing a qualitative assessment of the predictive performance of the PK (Fig. 2a) and PD (Fig. 2b) models. The predictive performance of the models can be evaluated relative to RN and NA (sum of all observed values divided by the number of observations). Plots with model predictions closely following observed data, compared to RN and NA, suggest that the neural network model achieved predictive learning during the training process. Figure 2a shows that the PK model created by neural network analysis appears to predict with precision REP AUCs for test subjects. This is readily

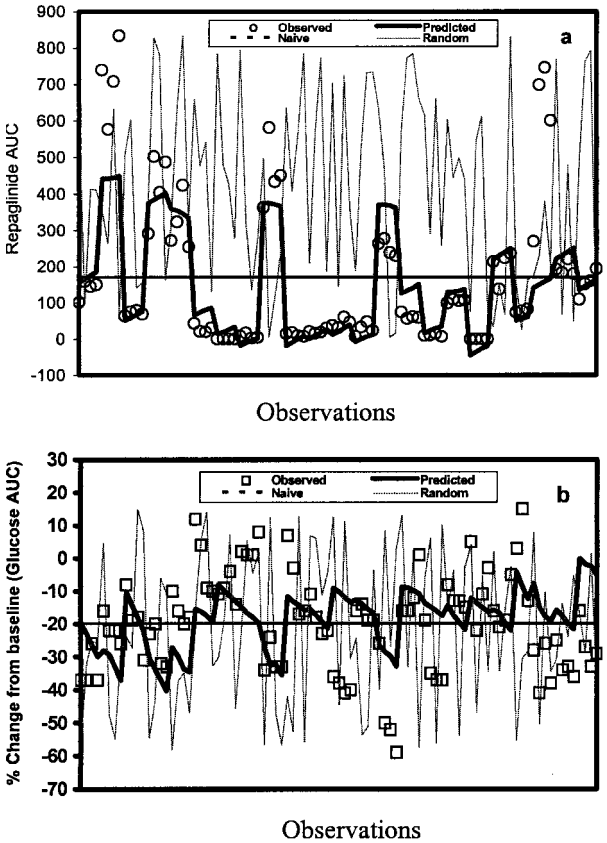

Fig. 2. Model predictions (–) for the test data set across observed values (symbols) of Repaglinide AUC (a) and % change from baseline for Glucose AUC (b); this figure provides a quick assessment of the models' pharmacokinetic and pharmacodynamic predictive performance relative to naive averaging of data and randomly generated numbers.

apparent when the predicted plot is compared to the plots generated by NA and RN.

In Figure 2b, however, the PD model appears to predict observed response with less precision when compared with the PK model. The model was less successful in predicting percent change from baseline (glucose AUC). This may be attributable to the variable nature of glucose control, where multiple physiologic and unknown factors can influence glucose levels.

Table I provides a comparison of the predictive performance of the PK and PD neural network models. It lists precision (RMSE) and bias (ME) values, plus their 95% confidence intervals, for the training and test data sets. In Table II, the precision and bias of the neural network models are compared with NA and RN. This provides a comparison of the predictive performance of the PK and PD models created by ANN analysis relative to NA of data and RN. It should be noted that the precision and bias values listed in Table II are those of the test data set because it consists of data that were not used in model development. This allows for an unbiased comparison between the three approaches (ANN, NA, and RN).

The relative importance of different covariates was determined using a genetic algorithm. The results are shown in Figure 3a for the PK model and Figure 3b for the PK–PD model. In Figure 3a, week of treatment appears to have the

Table I. Neural Network Predictive Performance: Comparison of Root Mean Square Error (RMSE) and Mean Error (ME) and Confidence Intervals for the Training and Test Sets

	Training	Test
Pharmacokinetic		
RMSE	113	125
95% CI	(89, 132)	(67, 163)
ME	0.0	22.6
95% CI	(–10.6, 10.6)	(–2.7, 47.9)
Pharmacokinetic-pharmacodynamic	Training	Test
RMSE	15.7	14.3
95% CI	(14.0, 17.2)	(12.4, 15.9)
ME	0.0	–1.3
95% CI	(–1.4, 1.5)	(–4.2, 1.7)

least effect on the PK parameter evaluated (REP AUC). This suggests an absence of drug accumulation and/or self-induced metabolism. The week of treatment, as well as race, appear to have little influence on the pharmacodynamic response (percent change from baseline for glucose AUC). Dose and weight, however, appear to predominate relative to the other covariates. This is consistent with the nature of the disease and its treatment.

The effect of weight, gender, and age on the exposure–response relationship for REP was evaluated using simulations. Figure 4a illustrates the effect of age on the REP AUC-Glucose AUC (percent change from baseline) in male patients using the lowest dose tested (0.25 mg REP). In Figure 4b, the same simulations are presented, but for female patients. The simulations were replicated using the highest dose (4 mg REP). The results are shown in Figure 5a for males and Figure 5b for females. In the simulations, all covariates were kept constant with exception of the covariate under evaluation (e.g., age). The latter was varied over a range representative of the data. It should be noted that the range for REP AUC (x-axis, Figs. 4 and 5) was higher for women relative to men. This reflected the observation that women had higher REP blood levels compared to men.

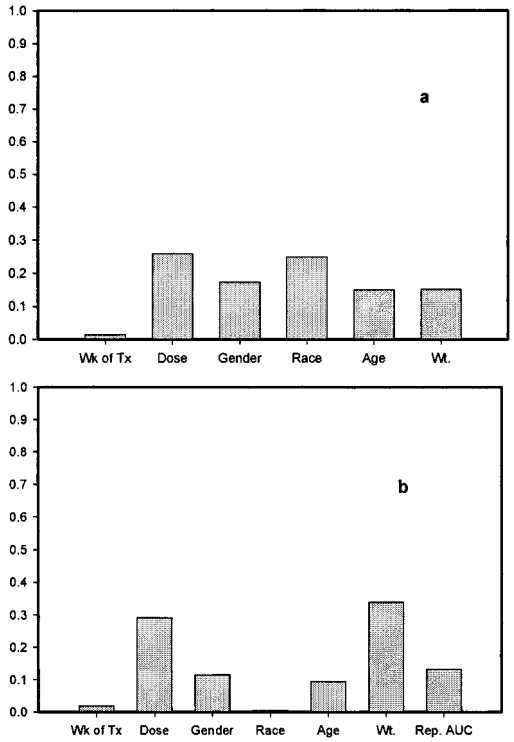

Fig. 3. Relative significance of patient covariates, on a scale between 0 (no contribution to predictive model) and 1 (total contribution) for the pharmacokinetic (a) and pharmacodynamic (b) models.

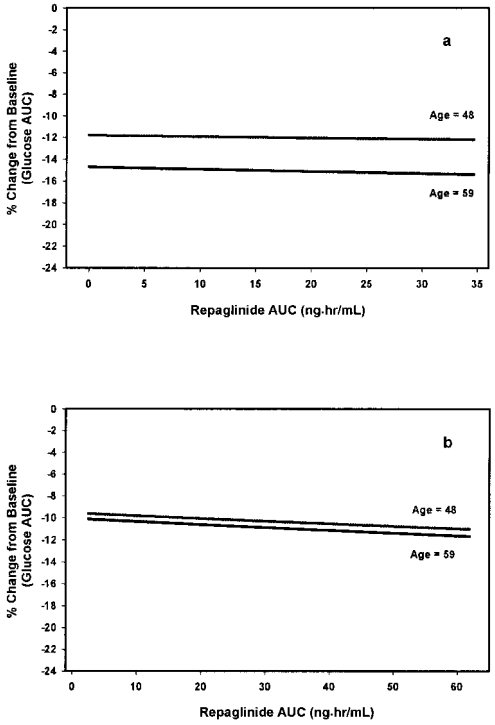

Fig. 4. Simulations showing change from baseline glucose AUC as a function of repaglinide AUC in men (a) and women (b) for the 0.25 mg dose of repaglinide. The effect of age (within the range of the data) is also shown.

Finally, Figure 6 illustrates dose–response plots for males and females. Percent change from baseline for glucose AUC is plotted as a function of the four REP doses used in the clinical trial.

DISCUSSION

The PK model created by ANN analysis predicted with precision REP AUC in the test data set, which was naive to the model. Visual inspection of the model prediction plot (Fig. 2a) showed that the model achieved learning during the training process that was generalized to the test data set. The model was clearly more predictive than NA of the data or RN. This was confirmed after the calculation of precision and bias values for the training as well as the test data sets.

Evaluation of the predictive performance of the PK–PD model, using visual inspection of model predictions in Fig. 2b, suggests that model performance was not as precise relative to the PK model. The model prediction plot seems to "miss" a good number of observations (percent change from baseline for glucose AUC), suggesting less learning was achieved during the training process. This may result when the appropriate covariates are not identified for model development, and/or

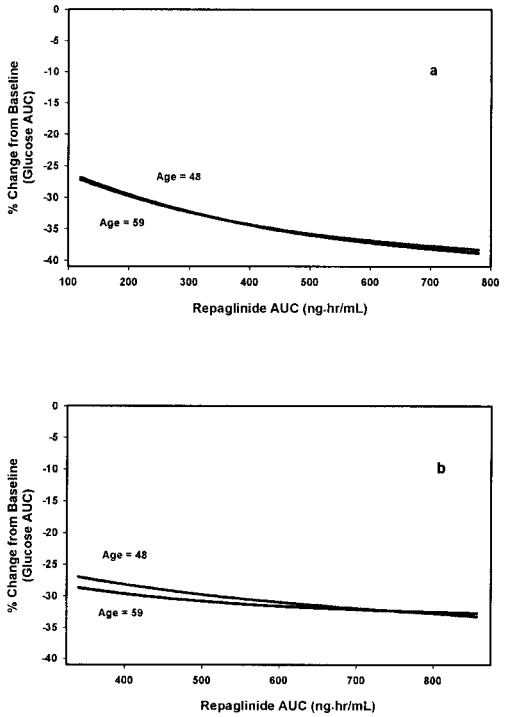

Fig. 5. Simulations showing change from baseline glucose AUC as a function of repaglinide AUC in men (a) and women (b) for the 4-mg dose of repaglinide. The effect of age (within the range of the data) is also shown.

when insufficient data is available for training. The former is more likely true for this study, given what we know about the variable nature of glucose control in type 2 diabetes. For example, numerous known and unknown factors, in addition to drug therapy, contribute to changes in glucose levels in a patient. Therefore, a good PK–PD model, using glucose levels as the PD endpoint, is difficult to obtain.

Predictive performance values listed in Table I show good precision with minimal bias when test sets are compared to their respective training sets. This is true for both the PK as well as the PK–PD model. A large RMSE value relative to the observed values would indicate poor model performance. Additionally, a large ME value, which can be greater than or less than zero, is diagnostic of systemic bias in model predictions. These two parameters are compared for the models obtained by ANN analysis, NA, and RN in Table II. For the PK model, ANN predictions were more precise than NA and significantly better than RN (RMSE of 125 vs. 204 and 429, respectively). In terms of bias, ANN performed reasonably well relative to NA, which by definition has zero bias, and it performed significantly better than RN.

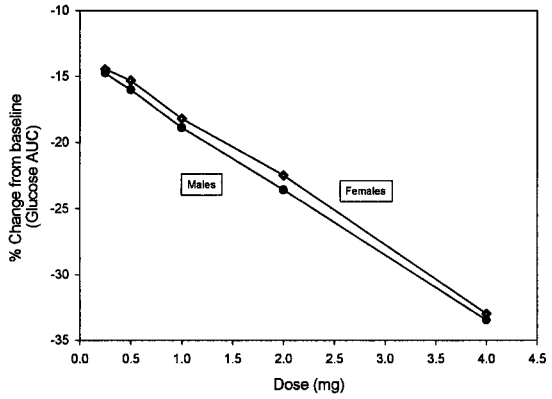

Fig. 6. Model predicted dose–response relationship for repaglinide in male and female patients with type-2 diabetes.

If we compare RMSE values for the PK-PD model across different methods (ANN, NA, and RN), it is readily apparent that ANN did not perform significantly better than NA (RMSE of 14 vs.15, respectively). This is another indication that the PK–PD model achieved less learning during training relative to the PK model. Again, this can be attributed to the difficulties associated with the use of glucose levels as a PD endpoint. Evaluation of bias measurements (Table II) for the PK–PD model reveals similar bias estimates across the three methods.

In addition to creating PK and PK–PD models using ANN, the relative importance (on a scale of zero to one) of the different covariates used in model building was evaluated by the genetic algorithm component of NeuroShell Predictor™. The covariates evaluated for the PK model included week of treatment, dose, gender, race, age, and weight. The results as shown in Fig. 3a indicate that the week of treatment had least influence on the pharmacokinetics of REP. This suggests that over the 4-week study period, no significant accumulation, induction, or inhibition occurred. The other covariates had some influence on the PK, although none were as predominant.

Covariates used in the development of the PK–PD model included week of treatment, dose, gender, race, age, weight, and REP AUC. Analysis by the genetic algorithm of the software indicated that week of treatment had little or no effect on REP PD. The relatively small contribution of the week of treatment, as is illustrated in Fig. 3b, suggests no significant tolerance to drug effect developed over the course of the study. Similarly, race did not appear to have a significant influence on the PD of REP. Dose and weight, on the other hand, seem to have the most significant contribution relative to the other covariates. The former would suggest a dose–response relationship, whereas the latter reflects what is known about the effect of body weight on glucose levels.

The effect of selected covariates on the exposure–response relationship of REP was evaluated through simulations (Figs. 4 and 5). The PK–PD model created by ANN was used for the simulations. Holding all covariates constant, response was simulated over a range of AUCs represented by the data for the lowest and highest dose. Exposure–response plots were generated to evaluate the effect of gender and age. The ranges for age selected for the simulations represented

Table II. Precision (RMSE) and Bias (ME) Comparison between Neural Network Analysis, Naïve Averaging of Data, and Randomly Generated Numbers for the Test Data Set

	ANN	NA	RN
Pharmacokinetic			
RMSE	125	204	429
ME	22.6	0.00	−244
Pharmacokinetic-Pharmacodynamic			
RMSE	14	15	27
ME	−1.28	0.00	1.49

data-rich regions of the data set used for training. Extrapolation to outside of the data range was avoided.

The results for the lowest dose (Fig. 4, a and b) suggest a slightly greater response for male patients relative to female patients. The same trend was seen for the higher dose as well (Fig. 5, a and b). It is interesting to note that females had greater exposure (AUCs) at similar doses. The PD response, however, was less than that of males. This is consistent with the determination by the genetic algorithm that in this study, dose was more important than AUC in determining response (Fig. 4b). The gender differences seen in PK as well as PD were not deemed clinically significant.

Finally, dose–response curves for REP were generated holding all covariates constant except for gender. The graph shown in Figure 6 seems to confirm the absence of a clinically significant, gender-based difference in PD. This conclusion is consistent with results from studies conducted by Novo Nordisk using traditional statistical analysis.

In conclusion, the use of ANN (NeuroShell Predictor™) to create PK and PK–PD models was fast, relatively easy, and yielded results that were consistent with traditional methods. Additionally, this approach was useful for generating hypothesis and evaluating "what-if" scenarios. The PK model performed better than the PK–PD model in terms of precision of predictions, although both models did well with regard to bias. Female patients had larger AUCs on average, relative to male patients; however, the differences in PD response were not clinically significant.

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