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; and 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 secretagogue, unrelated to the sulfonylureas, which was approved for the treatment of type-2 diabetes mellitus in 1998. Repaglinide (REP) differs from other insulin secretagogues, 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 Ca2+ channel opening, Ca2+ 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...
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 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