Neural Network Predicted Peak and
Trough Gentamicin Concentrations

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Predictions of steady state peak and trough serum gentamicin concentrations were compared between a traditional population kinetic method using the computer program NONMEM to an empirical approach using neural networks. Predictions were made in 111 patients with peak concentrations between 2.5 and 6.0 μg/ml using the patient factors age, height, weight, dose, dose interval, body surface area, serum creatinine, and creatinine clearance. Predictions were also made on 33 observations that were outside the 2.5 and 6.0 μg/ml range. Neural networks made peak serum concentration predictions within the 2.5-6.0 μg/ml range with statistically less bias and comparable precision with paired NONMEM predictions. Trough serum concentration predictions were similar using both neural networks and NONMEM. The prediction error for peak serum concentrations averaged 16.5% for the neural networks and 18.6% for NONMEM. Average prediction errors for serum trough concentrations were 48.3% for neural networks and 59.0% for NONMEM. NONMEM provided numerically more precise and less biased predictions when extrapolating outside the 2.5 and 6.0 μg/ml range. The observed peak serum concentration distribution was bimodal and the neural network reproduced this distribution with less difference between the actual distribution and the predicted distribution than NONMEM. It is concluded that neural networks can predict serum drug concentrations of gentamicin. Neural networks may be useful in predicting the clinical pharmacokinetics of drugs.

KEY WORDS: neural networks; NONMEM; pharmacokinetics; prediction; gentamicin.

INTRODUCTION

Pharmacokinetic models predict plasma drug concentrations based on theoretical models of drug distribution and elimination. They require assumptions about the physical principles and laws governing the system. This theoretical approach fails when these underlying laws or principles are not sufficiently understood or known to be encoded into a set of relationships. Neural networks use an empirical approach for prediction and are based on observations of the system to discover relationships from the system’s recorded behavior.

Neural computing is an attempt to build mathematical models that mimic the computing power of the human brain.

Therefore, the terminology and graphical representations of neural computing are similar to the nervous system. A comprehensive and detailed analysis of the multilayer feed forward network that was used can be found elsewhere (1). A detailed mathematical discussion of neural networks in applied pharmacology has been reported by Veng Pedersen and Modi (2).

A neural network was used to predict peak and trough gentamicin serum concentrations based on empirical data and compared these results to predictions using nonlinear mixed effect modeling (NONMEM). The hypothesis that neural networks are capable of predicting peak and trough serum concentrations with bias and precision equal to that of a NONMEM approach was tested. Gentamicin is used as a model drug which follows linear pharmacokinetics and for which the relationship between the pharmacokinetic parameters and covariates are known.

METHODS

This study was performed on data obtained from the clinical dosing services of the Veterans Administration Medical Center (VAMC) in Louisville, KY. Data were collected on 144 patients who had received gentamicin and for whom the pharmacy was consulted for dosage adjustments. The information recorded was the patient’s age, height, weight, serum creatinine, dose, dose/weight, dose interval, peak serum gentamicin concentration, and trough serum gentamicin concentration. Some patients received several different steady-state doses of gentamicin and had corresponding peak and trough concentrations. These new doses were treated as new patients for the purpose of prediction. All patients were male and had both a measured peak and trough gentamicin serum concentration. The actual timing of the peak and trough samples were not recorded in all of the patients. Therefore, the timing of all the peaks for the analysis were set to 1 hour after the beginning of the infusion and troughs at the end of the dosing interval. Values for creatinine clearance (Clcr) and body surface area (BSA) were calculated using the following formulas (1):

\[\text{Clcr} = \frac{140 - \text{age}}{\text{Scr}} \]

\[\text{BSA} = \frac{(\text{weight})^{0.425} \times (\text{height})^{0.725} \times 71.84}{10,000} \]

where Clcr is in ml/min/1.73m², BSA is in m², Scr is in mg%, weight is in kg, and height is in cm. The dosing interval was encoded into two new variables named “eight” and “twelve”. The variable “eight” had a value of 1 if the dosing interval was every eight hours and 0 if the dosing interval was every twelve hours. The variable “twelve” was coded to be opposite the value of variable “eight”.

The data were examined to determine the distribution of peak concentrations within the population as shown in Figure 1. From these data a subset was constructed containing peak concentrations between 2.5 and 6.0 μg/ml where sufficient data exist to train the neural network and was called the training range. This subset was formed since neural ne...
work training relies on sufficient data distributed through the output range. The network may not predict well in areas where there are few data with which to train the network. Concentrations greater than 6.0 \( \mu g/ml \) or less than 2.5 \( \mu g/ml \) were predicted following the development of the neural network and NONMEM models to test the ability of these methods to extrapolate outside of the training range. The training range contained 111 observations. These 111 observations were sorted by peak concentration in ascending order. The data were then divided into five data sets (DS1-DS5) containing approximately 22 records each. The peak distribution of data in each of the data sets was as nearly the same as possible.

Four of the five data sets described in the above paragraph were used to create a training data set containing approximately 89 peak and trough pairs along with the corresponding dosing information and covariates. The data set that was withheld was used for testing and contained approximately 22 peak and trough pairs along with the corresponding dosing information and covariates. This process was repeated a total of five times so that all the data were withheld from training at some time. This resulted in 5 training data sets and 5 testing data sets. The neural network used the training set to adjust the weights of the input variables. NONMEM used the training set to determine the population values of clearance and volume of distribution.

**Neural Networks.** The basic processing element in neural computing is the neuron. The neuron is responsible for the summation of all weighted inputs and either the linear or nonlinear mapping performed on this weighted sum. Neural Works Professional II/Plus version 5 (Neural Ware, Pittsburgh, PA) was used to create the neural networks. A feed-forward, multilayer neural network with a modified learning rule, extended delta bar delta as the error back-propagation technique was constructed (2,3). A hyperbolic tangent was used as the transfer function. Inputs to the neural network consisted of age, height, weight, dose, dose interval, dose/weight, eight (0,1), twelve(0,1) serum creatinine, creatinine clearance, and body surface area. A hidden layer of 5 neurons which was fully connected to the input and output layers was used. The output layer was a single neuron and predicted either peak or trough serum gentamicin concentration. Separate neural networks were created for the prediction of peak concentrations and for the prediction of trough concentrations. The outputs from each neuron propagated in one direction from the input through the hidden layer to the output layer with no recirculation. The error that occurred when the network predicted output was different from the measured output was used to adjust the weights of the network by means of back-propagation. Back-propagation is the process of dividing the responsibility for the prediction error back through the network and performing meaningful weight adjustments. The weights operated as the memory components of the network and were modified to improve prediction. One group of networks was developed with the output layer consisting of one neuron for the prediction of peak concentrations and a second group of the prediction of trough concentrations. This network architecture is shown in Figure 2.

There are three phases in neural computing: training, testing, and applying. During the training phase, the weights that connect the neurons are adjusted to predict the desired output. Supervised training, where the network was shown input data with the associated outputs during training was used. Data from the training set were presented to the network and the average error was computed over an epoch. An epoch is the number of training steps performed, over which the mean training error is computed. Several epoch sizes were evaluated in order to improve convergence rate and avoid local minimum. In general, epoch sizes much less than 75 resulted in divergence of the neural network and epoch sizes much greater than 75 resulted in memorization of the training set and a subsequent loss in the ability to generalize. The weights were adjusted at the end of the epoch. The network weights were repeatedly adjusted until the objective function was minimized or by limiting the number of training records presented to the network to 100,000. The objective function used was root mean square error. The root mean square error is the square root of the mean squared prediction error. The weights were then fixed and the testing phase began.

During the testing phase, the network was tested for its ability to generalize to the prediction of serum gentamicin concentrations on data not seen by the network previously. Test data were presented to the network in one pass. The network predicted peak or trough serum gentamicin concentrations. The prediction error was calculated to determine the ability of the network to generalize on the new data.

![Fig. 2. Multilayer, feedforward, neural network design used in the prediction of gentamicin serum peak or trough concentrations.](image-url)