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 multimodal 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):

$$Clcr = \frac{140 - age}{Scr} \qquad \text{equation 1}$$

$$BSA = \frac{(weight)^{0.425} * (height)^{0.725} * 71.84}{10{,}000} \qquad \text{equation 2}$$

where Clcr is in ml/min/1.73m^2, BSA is in m^2, 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 net-

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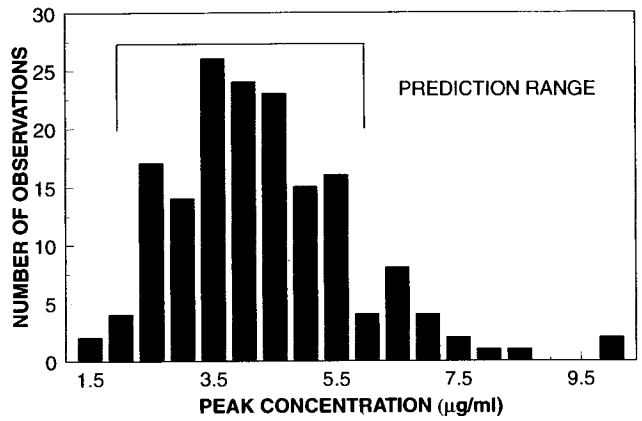


Fig. 1. Distribution of peak gentamicin serum concentrations in 144 patients with the training range shown between 2.5 and 6.0 μg/ml.

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 μg/ml or less than 2.5 μg/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 combined 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 feedforward, 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.

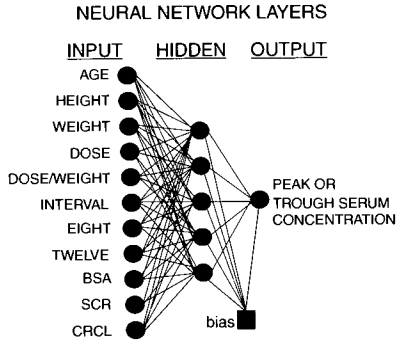


Fig. 2. Multilayer, feedforward, neural network design used in the prediction of gentamicin serum peak or trough concentrations.

During the application phase the neural network weights are fixed and the model is used to predict future events.

Peak and trough gentamicin predictions were performed by different networks. Five networks were created for the prediction of peak concentration and five networks were created for the prediction of trough concentration. Peak neural network 1 was trained with data from DS2-DS5 and tested with DS1, trough neural network 5 was trained with data from DS1-DS4 and tested with DS1. All data were tested in a similar fashion. Final predictions were combined into one file for testing.

Population kinetics. The predictive performance of the neural network has compared to predictions based on population estimates (4). The population pharmacokinetic analysis was performed using nonlinear mixed effects modeling as implemented by NONMEM version 4. Fixed effects, the predictors used in the neural network development, were added to the model and tested for their significance in decreasing the objective function. These covariates tested in the NONMEM model were age, height, weight, dose, dose interval, dose/weight, serum creatinine, creatinine clearance, and body surface area. Initially, a two compartment model was tested but NONMEM was unable to provide meaningful estimates for several of the pharmacokinetic parameters. A one compartment model (ADVAN1) with an additive error model was most descriptive of the data. A proportional error model was tested but did not perform as well as the additive model. The same data that was used for the training of the neural network was used to determine the population pharmacokinetic parameters using NONMEM. The final NONMEM model is shown below:

$$\begin{aligned} TVCL &= \theta_1 + \theta_3 * Crcl \\ TVV &= \theta_2 + \theta_4 * WEIGHT \\ CL &= TVCL*(1+\eta_1) \\ V &= TVV*(1+\eta_2) \\ Y &= F + \epsilon_1 \end{aligned} \qquad \text{equation 3}$$

where TVCL, is the typical value of clearance; TVV, is the typical value of volume of distribution; CL, is clearance; V, is volume of distribution; θ, η, and ϵ are model parameters; Y, is the observed concentration; and F is the model predicted concentration. After the final model was determined and converged, the initial estimates were set equal to the final estimates, the maximum number of evaluations was set to 0, the data set was switched to the test data set, and population based predictions were obtained on the test data sets labeled DS1-DS5. Population predictions for the test set were recorded following the NONMEM evaluation. Five predictions were performed on DS1-DS5 using the population parameters determined from fitting the remaining four datasets that were combined to create the training data set.

Statistical Analysis. A statistical analysis of the predictions for the measurement of precision and bias were performed. The following formula and abbreviations are those used by Sheiner and Beal (5). The prediction error (pe) was calculated as the prediction—observed for each of the N observations. Mean prediction error is a measure of bias and imparts information about the relative over- or under-prediction of the method used. Mean squared prediction error (MSE) and root mean squared prediction error (RMSE) were used as the measures of precision calculated as:

$$MSE = \frac{1}{N}\sum_{i=1}^{N} pe_i^2 \; ; \; RMSE = \sqrt{MSE} \qquad \text{equation 4}$$

Precision gives information about the size of the miss in prediction. Mean prediction error (ME) was used as the measure of bias and it was calculated as:

$$ME = \frac{1}{N}\sum_{i=1}^{N} pe_i \qquad \text{equation 5}$$

PE was also reported as a percentage of the predicted value and as the absolute value of the pe as:

$$pe(\%) = 100\frac{prediction - observed}{prediction} \qquad \text{equation 6}$$

$$|pe(\%)| = 100\frac{|prediction - observed|}{prediction} \qquad \text{equation 7}$$

Varvel calculated four statistical measures of performance of a predictive system for computer controlled infusion pumps (6). These measures were also calculated as they would apply to this specific prediction problem. Absolute performance error (APE) is another name for the absolute prediction error and is calculated as in equation 7. The median value of APE was reported to overcome the effect of any asymmetric distribution of the absolute value of the prediction error data. APE is a measure of precision. The slope of the linear regression of pe(%) versus the predicted value was used as a measure of divergence. Divergence is a measure of the expected systematic concentration-related deviation in the data. Varvel et al. calculated divergence using the absolute value of the prediction error. Divergence was calculated on these data as a regression of pe vs. predicted. Median prediction error (MDPE) was used as a measure of bias. Measures of bias (ME) and precision (RSE, APE) were tested by a paired t-test.

Density estimates were calculated on the observed, neural network predicted, and NONMEM predicted peak and trough gentamicin serum concentrations using S-PLUS version 3.1 (Statistical Sciences, Inc., Seattle, WA). Density plots were made with the width parameter set equal to 1.

RESULTS

The distribution of serum gentamicin peak concentrations in the 144 subjects are shown in Figure 1. One hundred eleven of these subjects had peak concentrations between 2.5 and 6.0 μg/ml and were used for training the neural network or fit using NONMEM. Table I contains a list of the descriptive statistics for the predictors in the 111 patients used in the neural network or NONMEM model. Figure 3 shows the prediction results of the cross validation experiments where 4/5 of the data were used to train or fit and 1/5 of the data were predicted for peak and trough concentrations. Figure 4 illustrates the resulting residuals of these predictions. Regression of the residuals against predicted concentration as a measure of divergence was performed. Both prediction methods resulted in over-prediction at low peak

Table I. Descriptive Statistics of the Predictors Used in the Neural Network for the 111 Subjects Within the Training Range of 2.5–6.0 μg/ml Gentamicin Peak Concentration

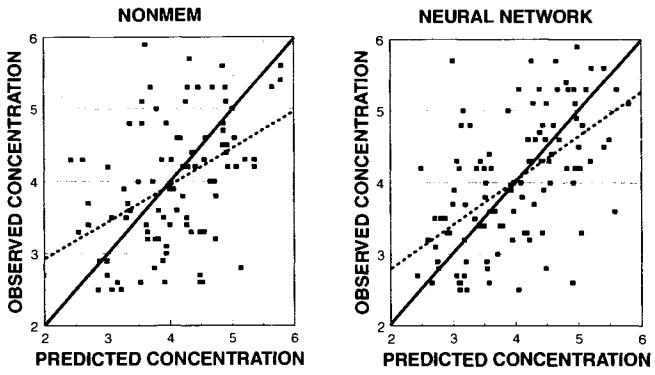
Predictor	Mean	Median	Range	STD
Age (yr)	64.2	66.0	31–85	11.0
BSA (m^2)	1.88	1.87	1.37–2.76	0.26
Clcr (ml/min/1.73 m^2)	77.4	73.5	19.0–163.0	26.2
Dose (mg)	88.7	85.0	40–150	23.1
Dose/wght (mg/lb)	0.58	0.54	0.24–1.25	0.17
Height (in)	69.6	70.0	63–76	2.9
SCR (mg%)	1.08	1.00	1.36–9.87	1.46
Weight (lb)	161.4	153.0	78.4–349.0	46.6

concentrations and under-prediction at high peak concentrations.

Table II upper panel lists the statistical measures used to make comparisons between the neural network and NONMEM predictions for the peak gentamicin serum concentration. Mean prediction error was used as the measure of bias and was tested by paired analysis. The neural network predictions in the training range were less biased than the NONMEM prediction ($p=0.037$). The average size of the difference in bias was 0.16μg/ml. Squared prediction error, root mean squared prediction error, or absolute prediction error were used as the measure of precision were tested by paired analysis. The neural network predictions were numerically more precise, but not statistically so ($p=0.058$). The average size of the difference in precision was 0.11 μg/ml.

Table II lower panel lists the statistical measures used to make comparisons between the neural network and NONMEM for the trough serum gentamicin concentration predictions. The mean prediction error was tested by paired analysis. The neural network trough concentration predictions were no less biased than the NONMEM predictions ($p=0.977$). The neural network predictions were no more precise than the NONMEM trough concentration predictions ($p=0.233$).

The density plots for the observed, neural network predicted, and NONMEM predicted peak and trough gentamicin serum concentrations are shown in Figure 5. The probability distribution of peak concentrations was complex, suggesting the presence of several modes. The neural network was better able to reproduce this complex pattern than was NONMEM. The probability distribution of trough concen-



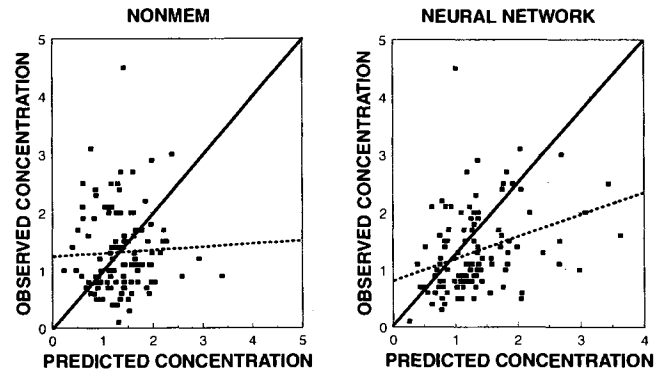
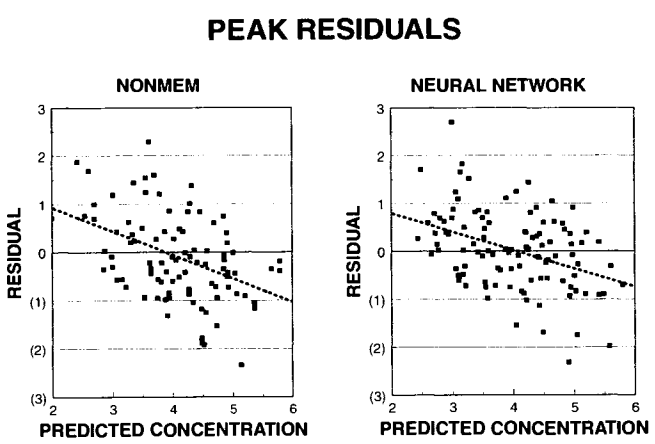


Fig. 3. Gentamicin serum peak and trough concentration predictions for both NONMEM and neural networks. Solid line represents the line of identity and dotted line represents the regression line. Concentrations are in μg/ml.



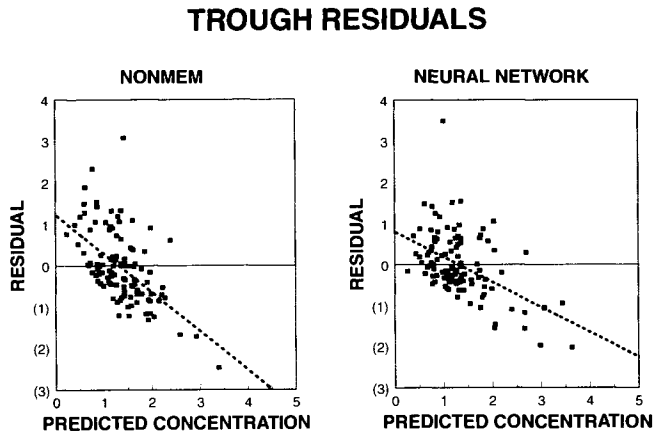


Fig. 4. Residual plot obtained from plotting predicted-observed for both NONMEM and neural networks. The dotted line is the regression line. In all cases, the regression line has a slope that is significantly different from zero. Concentrations are in μg/ml and negative values are shown within parenthesis.

Table II. Comparison of NONMEM and Neural Network Peak and Trough Gentamicin Serum Concentration Predictors Based on Training or Fitting with 4/5 of the Data and Prediction in 1/5 of the Data

	Peak predictions			
	NONMEM		Neural network	
	Mean (median)	95% CI	Mean (median)	95% CI
PE*	0.14 (0.22)	−0.03, 0.31	−0.02 (−0.03)	−0.18, 0.13
PE (%)	1.04 (5.54)	−3.42, 5.49	−2.45 (−0.69)	−6.62, 1.72
RSE (APE)+	0.74 (0.65)	0.64, 0.84	0.63 (0.56)	0.53, 0.73
SPE	0.83 (0.42)	0.63, 1.03	0.67 (0.31)	0.46, 0.87
APE (%)	18.6 (15.2)	13.7, 19.3	16.5 (13.5)	13.7, 19.3
	Trough predictions			
	NONMEM		Neural network	
	Mean (median)	95% CI	Mean (median)	95% CI
PE**	0.049 (0.163)	−0.115, 0.214	0.002 (0.138)	−0.145, 0.149
PE (%)	−14.5 (16.9)	−31.1, 2.2	−11.1 (9.8)	−23.8, 1.7
RSE (APE)+ +	0.67 (0.59)	0.57, 0.78	0.58 (0.43)	0.48, 0.68
SPE	0.76 (0.35)	0.52, 1.00	0.60 (0.18)	0.35, 0.86
APE (%)	59.0 (38.7)	46.4, 71.7	48.3 (36.0)	39.1, 57.7

* p = 0.036; +p = 0.058; **p = 0.977; + +p = 0.233.
Values shown are based on the predictions in 111 subjects.
PE, prediction error; SPE, squared prediction error; RSE, root squared error; APE, absolute prediction error; PE (%), percent prediction error; APE (%), percent absolute prediction error.

trations appeared uni-modal and skewed. Both the neural network and NONMEM were able to reproduce this distribution.

The ability of the neural network and NONMEM to predict outside the training data range was tested by predicting peak and trough gentamicin concentrations outside the range of 2.5-6.0 μg/ml. The NONMEM peak predictions were numerically less biased by a mean difference of 0.20 ± 0.69 μg/ml (p=0.073) and numerically more precise by a mean difference of -0.19 ± 0.63 μg/ml (p=0.098). NONMEM trough predictions were no less biased then the neural network with a mean difference of - 0.01 ± 0.85 μg/ml (p=0.942) and were numerically more precise by a difference of 0.19 ± 0.53 μg/ml (p=0.051).

DISCUSSION

Reidenberg recently summarized advances in clinical pharmacology (7). New drug compounds with unique mechanisms of action demand novel research approaches. Understanding the disease processes, the mechanisms of drug action, the relationships between patient and drug factors, and the response to therapy continue to be the compelling forces in clinical pharmacokinetics. Because clinicians must decide how much drug a patient should receive, prediction continues to be an important specialty for clinical pharmacologists. A new approach to prediction is described that is based on empirical relationships using a model drug, gentamicin.

To accurately forecast resulting drug levels, the entire drug dosing history, several aspects of the drug's disposition in the body, and various patient-related factors must be considered. As a result, prediction is a complex and multi-input, dynamic system. Computational intelligence stored in the neural network was used for the empirical prediction of dosing for gentamicin. The intelligence acquired from data driving the network learning was successful in predicting resulting drug concentrations. The neural network predictions matched the predictive performance of the NONMEM approach. Peak predictions were statistically less biased (p=0.036). The reason for the decreased bias may be related to the ability of the neural network to reproduce the complex distribution of peak gentamicin serum concentrations. The neural network predicted trough concentrations with the same bias and precision as NONMEM. When both methods were used to predict gentamicin concentrations outside of the range of data the NONMEM predictions were numerically more precise and less biased.

There are two primary approaches to prediction. Rules or equations can be developed to describe and predict a future state. Nonlinear mixed effects modeling is an example of a theoretical approach. This approach requires understanding the physical principles and laws governing the system, given the history of the system and its current state. However, this theoretical approach fails when these underlying principles are not sufficiently understood to be encoded into a set of relationships. The theoretical approach for predicting the dose of therapeutic agents depends on the use of pharmacokinetic models that mathematically describe the behavior of the drug in a test population. Often, this test population does not represent the population to which the drug is administered. When drug disposition does not follow

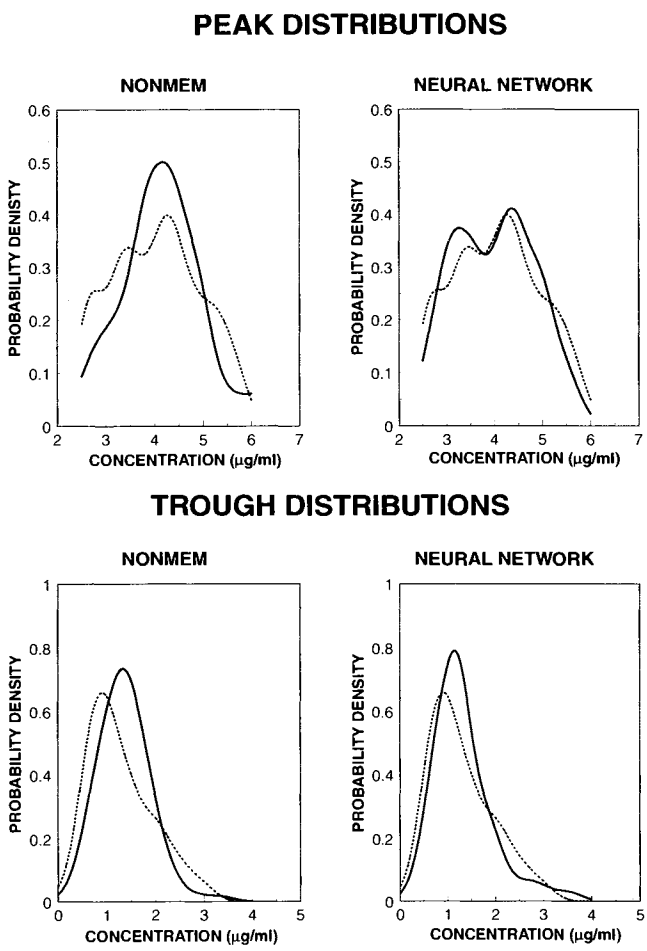


Fig. 5. Density plots of the peak and trough gentamicin serum concentrations from the observed data, the NONMEM predictions, and the neural network predictions. The dotted line is the observed density and the solid line is the predicted density.

these rigid rules, plasma drug concentrations and drug effects may be outside the therapeutic range. NONMEM was used since it is more flexible in determining the rules of drug disposition by employing a structural-statistical model and would represent a standard for comparison.

Mixed effect modeling has been applied to predicting the pharmacokinetics of gentamicin primarily in the pediatric population where it is useful in describing parameters like clearance and volume of distribution (8–11). Mixed effect modeling also accounts for the variability between patient by modeling the influence of covariates and residual variability. These previous studies have demonstrated how one might successfully model the effects of covariates like renal function and body weight with clearance and volume of distribution.

To avoid toxicity or therapeutic inefficacy, clinicians adjust dosages empirically. Empirical prediction relies on observation of the system and the discovery of relationships based on the recorded behavior of the system. A form of artificial intelligence, neural networks, is an example of an empirical method. This approach allows estimation of future values through processing many observations and discovering patterns in the data. The use of multiple and possible redundant inputs in the empirical approach allows the neural network to be less rigid than the theoretical approach. It is the additional information contained in these other inputs that allow the neural network to improve a prediction.

Investigators report successful applications of feedforward network architectures to such tasks as economic forecasting, as in the prediction of currency exchange rates and stock market trends (12,13), and technical forecasting, like helicopter gearbox failure and electric load distribution (14,15). Some studies demonstrate that neural network predictors offer a more flexible modeling environment than any of the traditional approaches, including statistical methods (16). Despite convincing results in many areas, little has been done using neural networks to predict drug behavior (17–19).

In the current report, a neural network approach for the prediction of drug levels has been compared to mixed-effects modeling. The neural network approach has several advantages. This is an empirical approach which does not require the relationship between the covariates and the prediction to be encoded. Neural networks do not require assumptions about the distribution of the data nor do the covariates need to be linearly independent or have a low correlation. Therefore, inputs can be used that are highly correlated such and age, serum creatinine, and creatinine clearance and inputs can be used that are linearly dependent like the variables eight and twelve. Use of input data that are redundant or coded in a binary fashion allows the network the flexibility to recombine the inputs in the hidden layer in order to improve prediction. Neural networks do not assume a model for the behavior of the system and can avoid the problems of model mis-specification. The disadvantage of the neural network is its inability to extrapolate outside the range within which it was trained while NONMEM can assume linear pharmacokinetics, apply a pharmacokinetic model, and perform this extrapolation. Neural networks are not used to describe the relationship between covariates and predictions like mixed effect modeling or to provide a reason for a particular observation. Rather, a neural network is used to predict future events given information which would be available at the time a physician sees a patient.

These data show that neural networks can be constructed to predict drug behavior, empirically. These networks performed well when compared to a traditional pharmacokinetic model of a drug that follows straight-forward, well known principles of disposition in the body. Neural networks can not be used to extrapolate outside the range for which they have been trained. The role of neural networks in predicting the behavior of those drugs which exhibit complex disposition remains to be determined as do their role in pharmacokinetic and pharmacodynamic modelling.

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