Neural Network Modeling to Predict the Hypnotic Effect of Propofol Bolus Induction

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ABSTRACT

Dose requirements of propofol to achieve loss of consciousness depend on the interindividual variability. Until now when propofol was administered by a single bolus, how to define the optimal individual dose and to assess its hypnotic effect have not been clearly studied. The goal of this study is to develop an artificial neural network model to predict the hypnotic effect of propofol on the basis of common clinical parameters. Ten parameters were chosen as the input factors based on the related literatures and clinical experiences. The bispectral index of EEG was used to record the consciousness level of patients and served as the output factor. The predictive results of neural net models were superior to that of clinician. This model could potentially help determine the optimal dose of propofol and thus reduce the anesthetic cost.

BACKGROUND

Due to its properties of rapid onset, short-acting, and fast recovery, propofol, an intravenous agent has been used for induction and maintenance of anesthesia as well as for sedation. Dose requirements of propofol to achieve loss of consciousness depend on the interindividual variability and on the interaction with other concomitant medications. Several studies had shown that the induction dose of propofol could be reduced up to 40 % in the elderly patients than the younger patients[1-3]. Maranets et al. have demonstrated that there was a moderate correlation between baseline anxiety and the amount of propofol required for the induction and maintenance of anesthesia[4]. Gan et al. reported that gender appeared to be an important variable in recovery from general anesthesia with propofol combined with alfentanil[5]. Many study groups have demonstrated that a variety of factors may alter the dose requirement of propofol for induction and maintenance of anesthesia, but in most studies the doses requirement of propofol and its pharmacodynamics and pharmacokinetics were studied under the target-controlled infusion system[6]. Until now when propofol was administered by a single bolus, how to define the optimal individual dose and to assess its hypnotic effect have not been clearly studied. Neural networks are statistical pattern-recognition tools composed of simple nonlinear processors connected into networks. In recent years neural networks had been widely used in computer-aided diagnosis[7, 8], in medical signal processing[9], and in cancer research[10]. In this study we used bispectral index of electroencephalogram (BIS) as the indicator of the hypnotic effect of propofol[11]. The goal of this study is to develop an artificial neural network model on the basis of common clinical parameters. We aim to demonstrate its ability in predicting the hypnotic effect of propofol bolus induction and compare the network output to the clinician's prediction.

METHODS

Study Population: Two hundred and seventy patients of American Society of Anesthesiologists physical status 1 or 2 undergoing elective surgery under total intravenous anesthesia were enrolled into this study. Patients who had documented drug allergy, who had currently known alcohol, drug, or medication abuse, or who had a history of psychiatric disorder were excluded. The local ethics committee had approved the protocols and informed consents from all the patients were obtained. One hundred and eighty patients were used to construct the neural network and were referred to as the training set. The remaining ninety patients formed the test set.

Study Setting: Age, gender, body weight, body height, and all available laboratory data were recorded for the further analysis. Baseline systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate, and hemoglobin oxygen saturation (SPO2) were recorded before induction of anesthesia (module 90489 on EKG Monitor-90303B, Spacelabs Medical, Inc.). Bispectral index of EEG was recorded continuously by the Ultraview Bispectral Index Module (Spacelabs Medical, Inc.).

All patients were allocated randomly to receive an individual bolus dose of propofol (1.6 mg/kg, 1.8 mg/kg, or 2.0 mg/kg) for anesthesia induction. The injection rate was controlled at the rate of 1 ml/s manually. No premedication was given. Two percent of xylocaine 2 ml iv was used preceding the propofol injection to ameliorate the injection pain. BIS values were recorded by an assistant who was blind to the induction dose of propofol and all the other parameters. The measurement of time was referenced to the end of the propofol bolus. After injection of propofol, the BIS values were recorded every 15 s and SAP, DAP, heart rate, and SPO_2 were recorded at 1-min interval for 5 min. Hypotension was defined as a 30 % decrease in SAP and was treated with repeated boluses of ephedrine. Respiratory status was monitored by an end-tidal CO_2 monitor (5250 RGM, Ohmeda). An episode of apnea more than 60 s was defined as significant respiratory depression and the patients were ventilated with face-mask until spontaneous ventilation returned.

Bispectral Index Monitoring: We used Bispectral index of EEG as the indicator of anesthesia depth and the hypnotic effect of propofol. Before BIS was introduced to clinical practice, depth of anesthesia was judged by patients' responses to oral command or by their hemodynamic responses to noxious stimulus. These responses were difficult to be quantified and were not the direct measurement of anesthesia depth. BIS was the first and only technology approved by the U.S. Food and Drug Administration (October 1996) for marketing as an EEG-based monitor of anesthetic effect. BIS does not specifically identify when a particular patient would regain consciousness but its capability to correlate with consciousness level has been extensively validated[11].

Design of the Artificial Neural Network: There were 10 parameters chosen as input factors by clinicians. The choice was based on the related literatures and clinical experiences. Input parameters used to train the artificial neural networks were shown in Table 1. We defined the BIS value of the 3rd min as the indicator of the hypnotic effect of propofol. When patients with the BIS value > 60 were considered as conscious awareness. For this study we chose to evaluate various networks each of which used the supervised back propagation training algorithm.

We used the NeuroShell 2 software (Release 3.0, Ward systems Group, Inc.) to train this model. The architectures selected in this study were the standard nets (one input layer, two hidden layers, one output layer) and the Ward nets (multiple hidden slabs with different activation functions). Learning rates and momentum terms were both automatically set as 0.1 and monitored by the software system.

Table 1. Input variables used to train the artificial neural networks

Propofol dose
Age
Gender
Body weight
Body height
Body mass index
Baseline SAP
Baseline heart rate
Hematocrit
Aspartate aminotransferase (GOT)

The entire data set of the training group was divided with a random number generator into 10 subsets. Nine of the 10 subsets were used for training and the 10th subset was used for calibration during training. The entire process was repeated 10 times by giving different random number seed. The mean square error was computed for each of the 10 neural networks. The mean square errors were averaged and the neural network that had a mean square error closest to the average was selected.

Performance Evaluation: The predictive model derived from the artificial neural network was validated on an entirely different data set that was not included in the training set. A receiver operating characteristic (ROC) curve was generated for the artificial neural networks. The ROC curve represents a graphical display of the true-positives (sensitivity) plotted against the false-positive (1-specificity) for various thresholds that defined the conscious awareness by the 3^{d} min of BIS value. Three senior anesthesiologists in our department were asked to make prediction of the same test set according to the ten input parameters. The results would be averaged and compared to those of well-trained artificial neural networks.

RESULTS

The models were designed to produce output values ranging from 0 (BIS value < 60) to 1 (BIS value > 60). The average mean squared error was 0.125 for standard nets and 0.114 for ward nets. The neural networks with the closest mean square error to the average were chosen for further analysis. The chosen standard nets had a sensitivity of 82.35 % and a specificity of 64.38 %. The chosen ward nets had a sensitivity of 80.00 % and a specificity of 58.46 %. The clinician made prediction for the 3rd min BIS >60 with a sensitivity of 20.64 % and a specificity of 92.51 % (Table 2). The area under ROC curve for the standard nets and ward nets were 0.7552 and 0.7274 respectively

(Figure 1).

Table 2. Comparison of the Clinician and Artificial Neural Networks Performance on the test set for the 3rd min BIS > 60 (n=90)

	Sensitivity (%)	Specificity (%)	Area under ROC curve
Standard nets	82.35	64.38	0.7552
Ward nets	80.00	58.46	0.7274
Clinician	20.64	92.51	0.5605

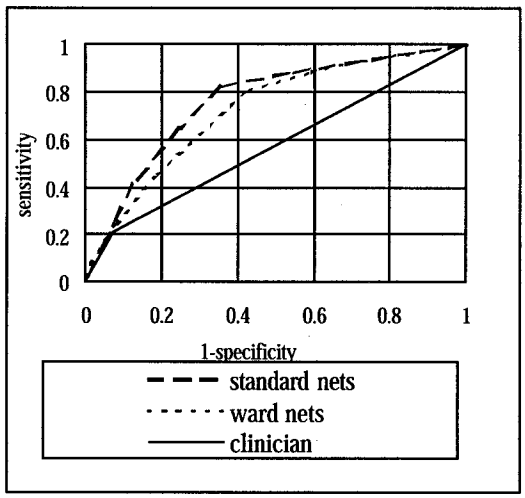

Fig 1. ROC curve for standard nets, ward nets, and clinician's results

DISCUSSION

If the higher doses of propofol were used for anesthesia induction it would be unnecessary to concern about awareness during the induction process. However, there was dose-dependent hemodynamic change associated with propofol induction. The hemodynamic data were present in table 3 and they were consistent with the clinical practice. When propofol dose increased the incidence of hypotension increased.

In our study we chose three induction doses based on body weight: 1.6 mg/kg, 1.8 mg/kg, or 2.0 mg/kg. Of the total 270 cases there were 58 cases (21.5 %) with BIS values > 60 for the 3rd min and 20 cases (7.4 %) with BIS values > 60 for the 2nd min. In this study we chose BIS as the indicator of consciousness. The patient with BIS > 60 meant the patient was conscious. Therefore the probability of undetected consciousness developed in anesthesia induction was not low. There were 4 and 12 cases developed a BIS value > 60 in the 2nd and 3rd min respectively even with the dose of 2.0 mg/kg. If difficult intubation was encountered during anesthesia induction, the patient might have become conscious with awareness while being paralyzed.

To our knowledge, this study was the first one to use a neural network for the prediction of hypnotic effect of propofol bolus induction. The induction dose of propofol was determined by a variety of clinical parameters. Age, gender, cardiac output, central blood volume, initial volume of distribution, and body mass index had been hypothesized to affect dose requirement of propofol by a number of reported studies. Schnider et al demonstrated the influence of age on propofol pharmacodynamics and concluded that elderly patients were more sensitive to propofol than younger patients[3]. Chassard coworkers indicated that the dose requirement of propofol was related to lean body mass (presented in body mass index, BMI) rather than to body weight[12]. According to the conclusions of the related studies and clinical experience we selected age, gender, body weight, body height, BMI, baseline SAP, heart rate, hematocrit, Aspartate aminotransferase (GOT), and propofol doses as the input parameters to construct the neural network model.

In the studies of Adachi and Kazama cardiac output and central blood volume were shown to be significant factors in the dose requirement of propofol[13, 14]. They suggested that in determining the induction dose of propofol, cardiac output and central blood volume should be considered as decisive factors. In our study we hoped to use the common and easy-accessible parameters as our input factors. Cardiac output and central blood volume were not included because they were not available in most patients.

In our study the neural networks demonstrated their ability to predict the hypnotic effect of propofol bolus induction. The predictive results of both neural net models were superior to that of clinician but might not be satisfactory when compared to other neural nets studies. The input parameters could not include all the key factors, e.g., cardiac output, central blood volume, and some unknown individual factors, which will obviously reduce the

Table 3. Hemodynamic data on three groups of patients

	Dose 1.6 (n=90)	Dose 1.8 (n=90)	Dose 2.0 (n=90)	Total (n=270)
Patients age (mean ± sd)	45.5 ± 14.1	43.2 ± 16.5	43.0 ± 16.5	43.9 ± 15.7
SBP decrease > 20%	19	22	45	86
SBP decrease > 30%	4	5	15	24

predicting power of this model When choosing the input parameters, we selected those being common and easily accessible to balance the accuracy of the model with its applicability in the clinical environment. If the selected parameters were difficult to obtain, the model would lose its clinical practicality. We were aware that many factors may affect the hypnotic effect of propofol, but in clinical practice most doctors decided the dosage only according to the patient's age and their past experiences. It was impossible for a doctor to consider all the related factors so it was not surprised that the clinician group had only 20.64 % of sensitivity in making prediction.

When propofol was administered for anesthesia induction, the pharmacodynamics and pharmacokinetics would be changed according to a variety of clinical parameters. When calculating the dose requirement of propofol, we should consider the individual condition of each patient. In this study we constructed the artificial neural network model to predict the 3rd min of anesthesia depth under propofol bolus induction. The model can potentially help determine the optimal dose of propofol and thus reduce the anesthetic cost. In the future we could enhance the sensitivity and specificity of this neural network by adding more important parameters. The dosing support system of propofol might be accomplished on the basis of this model to provide the optimal bolus dose to achieve the ideal induction endpoint.

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