Neural Network Modeling to Predict Intact Parathyroid Hormone in Uremic Patients on Continuous Ambulatory Peritoneal Dialysis

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Background: Measuring plasma intact parathyroid hormone (iPTH) concentration is essential to evaluate renal osteodystrophy. Although frequent measurement is needed to avoid inadequate prescription of phosphate binder and vitamin D preparations, it is not cost-effective in some clinics. For this purpose, we developed an artificial neural network (ANN) to predict plasma iPTH concentration in uremic patients on continuous ambulatory peritoneal dialysis (CAPD).

Methods: The study population consisted of 23 stable patients (11 male and 12 female, aged 48.8 ± 15.3 years) on CAPD for more than 3 months. Among ANN models, the predictors included plasma calcium, phosphate, alkaline phosphatase concentrations, and calcium-phosphate product. The dependent variable was plasma iPTH concentration measured by radioimmunoassay (RIA-iPTH). Leave-one-out cross-validation was adopted to iron out generalization problems caused by finite population. The least ratio of standard deviation (SDR) was used to choose the best ANN model. For comparing the performance between predictive plasma iPTH concentration by ANN (ANN-iPTH) and RIA-iPTH, the correlation coefficient (r), mean error, and Passing and Bablok regression were evaluated.

Results: The generalized regression neural network (SDR = 0.74) was the final best ANN model. The relationship between RIA-iPTH and ANN-iPTH is described by Passing and Bablok regression ANN-iPTH = 90.52 + 0.55 × RIA-iPTH, with 95% confidence interval for intercept 23.08 to 122.83 and for slope 0.30 to 1.16, indicating that both methods are interchangeable without statistically significant deviation ($P > 0.10$).

Conclusion: ANN can accurately predict plasma iPTH concentration in uremic patients on CAPD. It is useful and beneficial to assess renal osteodystrophy frequently and led to proper treatment.

Key words: neural network, intact parathyroid hormone, continuous ambulatory peritoneal dialysis

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Renal osteodystrophy includes several skeletal disorders that primarily occur in patients with renal failure. In general, these include high turnover bone disease (osteitis fibrosa and mixed lesions) due to persistently high levels of parathyroid hormone (PTH) and low turnover bone disease (osteomalacia and adynamic lesions) associated with relatively low levels of PTH. Obviously, PTH plays an important role in the pathogenesis of renal osteodystrophy. According to the K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease published by National Kidney Foundation [1], the guideline suggests that

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the frequency of measuring PTH should be monitored every three months in dialytic patients. Physicians and nephrologists will adjust the adequate prescription of phosphate binders and/or vitamin D preparations under the value of plasma PTH concentration to avoid further exacerbation in renal osteodystrophy.

An artificial neural network (ANN) consists of a set of processing elements which simulates the human neurons. These processing elements are interconnected via a set of "weights" analogous to synaptic connections in the human nervous system in a way which allows signals to travel through the network in parallel as well as serially [2]. ANN are applicable in virtually every situation in which a relationship between the predictor variables (independents, inputs) and predicted variables (dependents, outputs) exists, even when the relationship is very complex or not easy to formulate in the usual terms of "correlations" or "differences between groups". In other words, ANN provides a way to actively incorporate both past and present knowledge, to extract information, to map correlations and to produce inferences from available data. ANN has become well established as robust computational methodologies with reliable theoretic support and with strong potential to be effective in the fields of internal medicine [3-5] and nuclear medicine [6].

In past years, overt emphasizing the prevention of renal osteodystrophy increased the prevalence of adynamic bone lesions following the overuse of phosphate binders and vitamin D preparations. So it is reasonable to monitor plasma intact parathyroid hormone (iPTH) concentration measured by K/DOQI-recommended radioimmunoassay (RIA) frequently to guide the proper therapy in both hemodialysis and peritoneal dialysis patients but the cost will intensify the burden of health insurance in our country. The aim of present study is to evaluate the ability of ANN in predicting plasma iPTH concentration in uremic patients on continuous ambulatory peritoneal dialysis (CAPD). At the same time, these ANN models will be compared with plasma iPTH concentration measured by RIA, which is the current reference method used in clinical nephrology. To date with literature search in PubMed and the best of our knowledge, this is the first investigation using ANN to predict plasma iPTH concentration in uremic patients on CAPD.

Methods

We retrospectively analyzed our database of CAPD patients with a final study population of 23 stable patients (11 male and 12 female, aged from 16 to 76 years with an average age of 48.8 ± 15.3 years) on CAPD for more than 3 months. For the quantitative prediction of plasma iPTH concentration, we used the software package STATISTICA Neural Networks 6.0 (StatSoft, Inc., Oklahoma, US) to generate various formulations of ANN models. The automatic network designer decided an appropriate architecture, using a combination of heuristic and optimized approach. It conducted a large number of tests, which were used to decide the best architecture. It could automatically compare linear model, multilayer perceptron (MLP) model, radial basis function (RBF) model, generalized regression neural network (GRNN) model and automatically choose the smoothing factor and the number of units for these models [7,8].

To choose the adequate variables from monthly biochemical examination, we selected the most relevant parameters, used in clinical dialysis, such as plasma calcium (Ca), phosphate (P), alkaline phosphatase (ALP) concentrations, and Ca-P product to be the input variables in training ANN models. Plasma Ca, P, and ALP concentrations were measured by automatic biochemistry analyzer (Hitachi 7170; Hitachi Co., Tokyo, Japan) and plasma iPTH concentration was measured by RIA (Active I-PTH DSL-8000; Diagnostic Systems, Laboratories, Inc., Webster, TX, USA). All these plasma biochemistries were collected in the same month. The outcome variable was plasma iPTH concentration measured by RIA (RIA-iPTH) and the predicted output was estimated by ANN (ANN-iPTH).

For solving the statistical problem of finite patients in our study, leave-one-out cross-validation (LOOCV) was employed to avoid the possible bias introduced by relying on any one particular division into test and train components [9]. The LOOCV procedure involves removing one case from the training data; training is done on the basis of remaining data and then testing is done on this removed case. In this manner, if the training data consist of 100 cases, then 100 networks are produced by using each of the case as

test set while using the other case as the training data. This is the most extreme test of the cross validation. It is the most accurate way to estimate the performance of method when the training data is small. After training and testing in a regression problem of the ANN models, the ratio of the prediction error standard deviation (SD) to the original output data SD, called the ratio of SD (SDR), will be calculated by STATISTICA Neural Network. A lower SDR will give a better prediction in determining the final best ANN model.

Statistical analysis was performed using MedCalc for Windows 7.4.1.1 (MedCalc Software Inc., Mariakerke, Belgium). To test the performance of the estimates, ANN-iPTH was compared with RIA-iPTH using Pearson's correlation coefficient (r) and mean predictive error in Bland-Altman comparison [10]. The mean predictive error is an indication of bias and higher correlation means that the measurements by two methods are linearly correlated but this condition does not mean that the two methods agree. To compare the agreement and interchangeability of two methods, the Passing and Bablok regression describes a linear regression procedure with no special assumptions regarding the distribution of the samples and the measurement errors [11,12]. The result does not depend on the assignment of the methods to X and Y. The slope B and intercept A are calculated with their 95% confidence interval. These confidence intervals are used to determine whether there is only a chance difference between B and 1 and between A and 0. The significance level in this study was defined as $P < 0.05$.

Results

The final five networks were retained after training and validation of 1000 networks (Table 1).The best ANN model was a GRNN (SDR = 0.74), which had an input layer with 4 nodes, two hidden layers with 15 nodes and 2 nodes, and an output layer with 1 node (Figure 1). The results of selected biochemistries, RIA-iPTH, and ANN-iPTH were presented in Table 2. The RIA-iPTH and ANN-iPTH were 171.26 ± 40.99 and 198.73 ± 21.60, respectively which were not statistically different compared by performing paired t-test (P = 0.37).

The r value for the correlation between RIA-iPTH and ANN-iPTH was 0.70 (P = 0.0003). The mean predictive error was 0.82 (upper limit and lower limit of limits of agreement were 1.97 and -0.33, respectively) by using the ratio of

Table 1. The final five models of ANN after training and validation of 1000 networks

Network	Linear	MLP	RBF	RBF	GRNN
Variables of input layer	Ca, P, ALP, Ca-P	P, ALP, Ca-P	Ca, P, ALP, Ca-P	Ca, P, ALP, Ca-P	Ca, P, ALP, Ca-P
No. of hidden layers	0	2	1	1	2
No. of neurons in 1st hidden layer	0	4	1	3	15
No. of neurons in 2nd hidden layer	0	1	0	0	2
Variable of output layer	iPTH	iPTH	iPTH	iPTH	iPTH
SDR	1.19	0.86	1.00	0.96	0.74

Table 2. The results of selected biochemistries, RIA-iPTH, and ANN-iPTH

Biochemistries	Mean ± SE	Minimum	Maximum
Ca (mg/dl)	8.96 ± 0.25	6.68	10.96
P (mg/dl)	5.22 ± 0.28	2.90	7.60
ALP (IU/L)	146.33 ± 7.83	94.00	240.00
Ca-P product	46.52 ± 2.65	27.14	68.60
RIA-iPTH (pg/ml)	171.26 ± 40.49	9.64	828.70
ANN-iPTH (pg/ml)	198.73 ± 21.60	89.80	519.62

* SE: standard error of the mean.

RIA-iPTH and ANN-iPTH against average of RIA-iPTH and ANN-iPTH in Bland-Altman comparison. The significantly higher r value and less mean predictive error represented that the ANN model had less bias and high accuracy. In the Passing and Bablok regression, the relationship between RIA-iPTH and ANN-iPTH was described by ANN-iPTH = 90.52 + 0.55 × RIA-iPTH, with 95% confidence interval for intercept 23.08 to 122.83 and for slope 0.30 to 1.16, indicating that both methods are interchangeable without statistically significant deviation ($P > 0.10$).

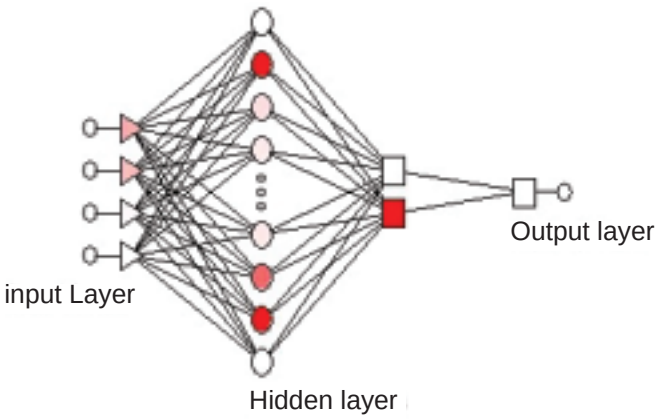

Figure 1. Topology of an (4 × 15 × 2 × 1) ANN model

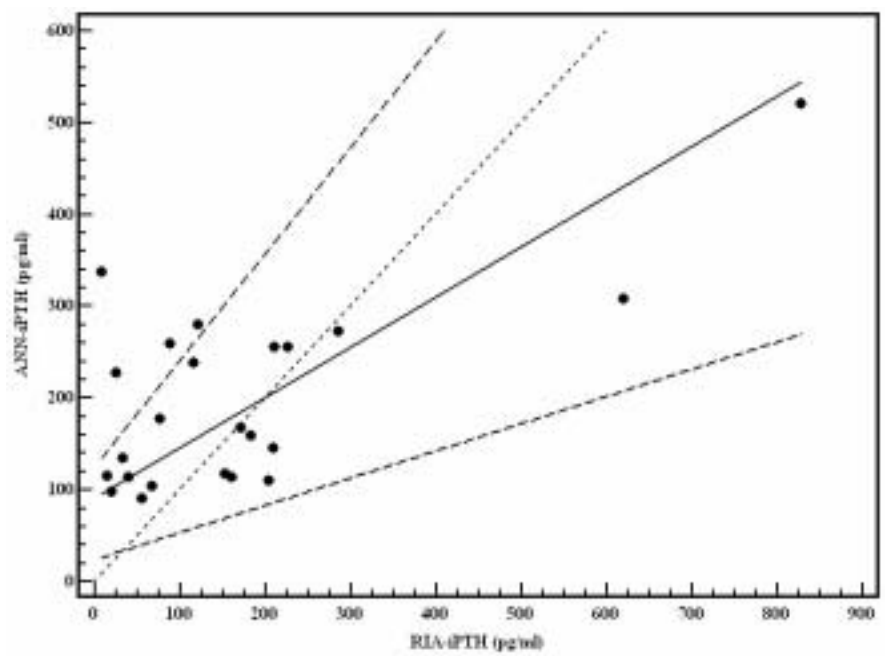

Figure 2. The Passing and Bablok regression shows a scatter diagram with the regression line (solid line), the confidence interval for the regression line (dashed lines) and identity line (x = y, dotted line).

We also used these four predictors in the multiple linear regression and its coefficient of determination was 0.16. Comparing correlation coefficient of ANN (r = 0.70) and multiple linear regression (r = 0.16) based on RIA-iPTH, the correlation was significantly higher in ANN ($P = 0.03$).

Discussion

In our study, ANN over plasma iPTH concentration in CAPD patients but it could predict plasma iPTH concentration accurately with less bias according to the results of mean predictive error in the Bland-Altman comparison and the Passing and Bablok regression.

The regulation of PTH in dialytic patients depends on the complicated interconnections among many contributors including age, gender, diabetes, duration on dialysis, renal function, Ca, magnesium (Mg), P, ALP, vitamin D, albumin, C-reactive protein, PTH gene transcription, skeletal resistance to the calcemic action of PTH, dialysis itself, metabolic acidosis, Ca sensing receptor, vitamin D receptor, and laboratory available protein markers etc. In previous study related to our study, Navarro JF et al. [13] utilized demographic data and several serum biochemistries (ALP, Ca, Mg, P, and albumin etc) of 110 CAPD patients to analyze the correlation between the iPTH. The results demonstrated that only P and Mg predicted iPTH values (iPTH = -35 — 135 × Mg + 23 × P, r = 0.59, $P < 0.001$) in multiple linear regression . In our study, for the purpose of simplification in clinical practice, we only selected three common biochemistries (Ca, P, and ALP) with Ca-P product, which are ordinary monitored in dialytic unit monthly, to predict the plasma iPTH concentration in the ANN model and the correlation was much better than the conventional multiple linear regression (0.70 vs. 0.16, $P < 0.05$). Comparing r values between ANN and the finding of Navarro JF, although the difference were not statistically significant (0.70 vs. 0.59, $P = 0.44$), our ANN model had higher value. In particularly,

the patients participated in our study were less than theirs. We took advantage of the LOOCV procedure, which is a kind of resampling method, to overcome this problem. Also, we employed just four predictors, still less than predictors used in theirs, to achieve the similar results. Although the r values were comparable in these two studies, this easy comparison could not truly represent which one is better. If the original data of the study by Navarro JF et al. is available, we could use the folded empirical cumulative distribution plot [14], Deming regression model [15], or Passing and Bablok regression to compare the superiority of these two studies.

Except the small numbers of study population, which was resolved by the LOOCV procedure to decrease the possibly internal bias, there were some notable limitations. First, although we used four predictors to obtain the better performance of ANN, we still expect more variables in the feature study. Second, our study was carried out at a single institute. The better protocol is to train the ANN model using the patients in an independent dialytic unit and validate other cases at another dialytic unit. The way for crossing multicenters study will decrease the bias further. Future studies will focus on developing the web-based platform using our ANN as kernel engine to let the clinicians to evaluate the plasma iPTH concentration in real time. Additional benefit is that the performance of ANN will be continuously improved over time when more data collected to retrain the ANN model.

Conclusion

We have illustrated that the use of ANN makes possible to obtain a good prediction of plasma iPTH concentration in CAPD patients. We can use this model to save the cost of the RIA if the clinicians want to monitor plasma iPTH concentration frequently. The quicker and more accurate in predicting plasma iPTH concentration by using ANN model, the more benefits and proper treatments could be brought to the CAPD patients. We deeply believe that ANN may be a useful tool for physicians and nephrologists to treat the CAPD patients in clinical practice.

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類神經網路模型預測連續性可攜式腹膜透析之尿毒症病患之完整副甲狀腺素

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背景：檢驗血漿完整副甲狀腺素濃度對於評估腎性骨病變非常重要。雖然多次檢驗能夠避免不適當地給予磷結合劑與維生素丁，但是在某些透析中心卻不符合經濟效益。本研究之目的爲開發人工類神經網路模型用以預測連續性可攜式腹膜透析之尿毒症病患的血漿完整副甲狀腺素濃度。

方法：本研究包括23位穩定之尿毒症病患 (11位男性，12位女性，平均年齡48.8 ± 15.3歲)，接受連續性可攜式腹膜透析療法超過三個月以上。在所有人工類神經網路模型中，預測因子包含血漿鈣離子濃度、磷酸根離子濃度、鹼性磷酸酶濃度與鈣磷乘積；而相依變數則是使用放射免疫法量測的血漿完整副甲狀腺素濃度 (RIA-iPTH)。因爲研究族群少，所以使用重新取樣之leave-one-out交叉效度法來避免此問題。再利用訓練完成後之人工類神經網路模型中，以最小的標準差比率選出最佳預測模型。最後，使用相關係數、平均差與Passing and Bablok迴歸分析法，來比較量測與預測 (ANN-iPTH) 的血漿完整副甲狀腺素濃度之差異。

結果：最佳人工類神經網路預測模型是使用以核心趨近法爲基礎之一般化迴歸類神經網路（標準差比率爲0.74）。量測與預測的血漿完整副甲狀腺素濃度之迴歸關係是ANN-iPTH = 90.52 + 0.55 × RIA-iPTH，其截距與斜率的95 %的信賴區間分別是23.08 到122.83與0.30 to 1.16，代表兩方法是可以互換的，並無統計學上的差異 ($P > 0.10$)。

結論：人工類神經網路可以精確地預測連續性可攜式腹膜透析之尿毒症病患的血漿完整副甲狀腺素濃度。對於評估腎性骨病變與施予適當治療，是一個有效益又好用的工具。

關鍵詞：類神經網路，完整副甲狀腺素，連續性可攜式腹膜透析

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