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Formulation of effects of atropine, pralidoxime and magnesium sulfate on cardiac tissue levels of nitric oxide, malondialdehyde and glutathione in organophosphate poisoning using artificial neural network

Necla Togun [a,*], Ataman Kose [b], Nurullah Gunay [c], Mehmet Tarakcioglu [d], Abdullah T. Demiryurek [e]

[a] Department of Mechanical Engineering, University of Gaziantep, 27310 Gaziantep, Turkey
[b] Emergency Department, Twenty-Five December State Hospital, Gaziantep, Turkey
[c] Emergency Department, Education and Research Hospital, Kayseri, Turkey
[d] Department of Biochemistry and Clinical Biochemistry, Faculty of Medicine, University of Gaziantep, 27310 Gaziantep, Turkey
[e] Department of Pharmacology, Faculty of Medicine, University of Gaziantep, 27310 Gaziantep, Turkey

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ABSTRACT

Anticholinesterase poisoning is an important health problem in our country, and a complete understanding of its underlying mechanisms is essential for the emergency physician. So, this study focused on two purposes. First one was aimed to investigate the biochemical analysis to determine the tissue levels of malondialdehyde (MDA), glutathione and nitric oxide (NO). Secondly, it was planned to model and formulate the effects of some drugs on cardiac tissues levels of NO, MDA and glutathione in acute organophosphate poisoning in rats by the application of neural network based on experimental results. It has been planned to determine whether artificial neural network (ANN) is appropriate tool to analyze and formulate it. As a result, it has been considered that ANN can be effectively used to model NO, MDA and glutathione level. The performances of ANN formulation versus target experimental values are found to be quite high. It is concluded that, proposed NN models are also presented as simple explicit mathematical functions for further use by researchers.

1. Introduction

Organophosphate (OP) compounds are the most widely used insecticides worldwide. So, poisoning with these compounds is especially an important environmental problem for developing countries [1]. Although accidental poisoning can occur after exposure to skin or inhalation, serious poisoning often follows suicidal ingestion [2]. These OP compounds act as powerful inhibitors of acetylcholinesterase (AChE), resulting in accumulation of acetylcholine and overstimulation of cholinergic synapses in the central nervous system, somatic nerves, parasympathetic nerve endings, and sweat glands [3]. The continued stimulation and eventual paralysis of the acetylcholine receptors account for the clinical signs and symptoms of OP poisoning (OPP), including muscarinic, nicotinic, and central nervous system effects [4].

Cardiac complications and sudden death in OPP may take place after the poisoning [3,5]. Various arrhythmias and conduction disturbances due to sympathetic and parasympa-thetic overactivity have been reported with OPP [6,7]. In addition, hypertension-hypotension, noncardiogenic pulmonary edema, and myocardial damage in a few cases have also been described [2]. The mechanism by which OP induces cardiotoxicity has not been elucidated thus far, and it is difficult to pinpoint 1 mechanism as being the cause of cardiac toxicity related to OP. There are a lot of investigations about the cardiac toxicity of OPP, but its pathogenesis and underlying mechanisms are not known [8–10].

Excessive reactive oxygen species (ROS) and lipid peroxidation (LPO) generation have been found to be involved in many diseases. Recent findings indicate that toxic manifestations induced by OP may be associated with an enhanced production of ROS. Some studies reported that OPP can cause LPO [11,12]. The experimental study have been performed in [13] about the effects of dichlorvos both on LPO of rat heart and the activities of some antioxidant enzymes.

The main drug used in standard therapy is atropine which antagonized the poisoning effects as muscarinic receptors. Pralidoxime used as an antidote has an important role in poisoning as inhibitors of acetylcholinesterase (AChE). In addition, it is reported that magnesium sulfate ($MgSO_4$) has been used on cardiac arrhythmia therapy in organophosphate poisoning [3].

This study provides an alternative approach for the formulation and the modeling of cardiac tissue levels of NO, MDA and

* Corresponding author. Tel.: +90 342 3172534; fax: +90 342 3601104.
E-mail address: nkara@gantep.edu.tr (N. Togun).

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glutathione in organophosphate poisoning using neural networks (NN). Artificial neural networks mimic somewhat the learning process of a human brain. Artificial neural networks have been used as a robust tool for the modeling and formulation of the cardiac tissue parameters due to the fact that these are widely accepted as a new technology offering an alternative way to tackle complex relationship that exists between dependent and independent variables [14].

2. Materials and methods

In the present study, male Wistar rats weighing 200–400 g were used. The experimental protocol was approved by the local ethics committee (Report no: 2005-06-09). Sixty-three rats were randomly divided into 6 groups. Control group (n=8) received corn oil, dichlorvos group (n=15) received 30 mg/kg of dichlorvos, Mg group (n=10) received 200 mg/kg of MgSO4 prior to dichlorvos, atropine group (A, n=10) received 10 mg/kg atropine prior to dichlorvos, pralidoxime group (PAM, n=10) received 40 mg/kg pralidoxime prior to dichlorvos, and A-PAM group (n=10) received 10 mg/kg atropine and 40 mg/kg of pralidoxime prior to dichlorvos. All drugs and vehicle were administered by intraperitoneally (i.p.) and after 6 h of injection, cardiac tissue samples were obtained. Biochemical analysis was performed to determine the tissue levels of malondialdehyde (MDA), glutathione and NO. Detailed explanation of experimental study can be found in Ref. [15].

Assessment of tissue samples: Tissue specimens were homogenized and centrifuged, and supernatant was analyzed for NO, MDA and glutathione levels. Tissue NO levels were measured by a NO/ozone chemiluminescence technique published by Alasehirli et al. [16]. To determine the tissue level of MDA lipid peroxidation (LPO) was estimated using the thiobarbituric acid reaction according to Ohkawa et al. [17]. Modified Ellman method [18] was used for cardiac tissue glutathione analysis, and the levels were measured using a spectrophotometer.

Statistical analysis: Statistical analysis was performed using GraphPad Instat (version 3.05). All data are expressed as mean $\pm$ SD or the percentage incidence. Statistical comparison of more than 2 groups was performed by a 1-way analysis of variance followed by Student-Newman–Keuls multiple comparisons test. A Fisher exact test was used to detect mortality difference between groups. Scores were analyzed using Kruskal–Wallis variance analysis. In all tests, P values of less than 0.05 were considered to be statistically significant.

2.1. Experimental results

Cardiac tissue levels of MDA, glutathione and NO were determined by using 63 male Wistar rats weighing 200–400 g. Cardiac tissue parameters and statistics of groups and control groups were given in Table 1.

Cardiac tissue NO levels were found to be statistically significant 93.5 ± 31.0 μmol/g wet weight in the magnesium group and 108.6 ± 44.5 μmol/g wet weight in the atropine+PAM group compared with 22.9 ± 6.6 μmol/g wet weight in the dichlorvos group ($p < 0.001$; Fig. 1), and no significant differences were found between the other groups. No significant changes were also observed with cardiac MDA and glutathione levels ($p > 0.05$; Fig. 2).

3. Neural network (NN)

Haykın defines a neural network as a massively parallel distributed processor. It has an inherent tendency for storing experimental knowledge and making it available for use. It resembles the human brain in two respects: the knowledge is acquired by the network through a learning process, and inter-

Table 1
Cardiac tissue parameters and statistics.

Groups	MDA (nmol/g tissue)	Glutathione (umol/g tissue)	NO (umol/g tissue)
Control (n=8)	1.2 ± 0.5	18.4 ± 6.1	19.7 ± 4.7
Dichlorvos (n=15)	1.4 ± 0.5	17.7 ± 3.2	22.9 ± 6.6
Magnesium (n=10)	1.8 ± 0.6	22.8 ± 3.7	93.5 ± 31.0
Atropine (n=10)	1.3 ± 0.4	17.0 ± 4.7	22.6 ± 11.5
PAM (n=10)	1.6 ± 0.6	22.3 ± 4.8	45.8 ± 33.6
Atropine+PAM (n=10)	2.0 ± 0.7	20.3 ± 7.0	108.6 ± 44.5

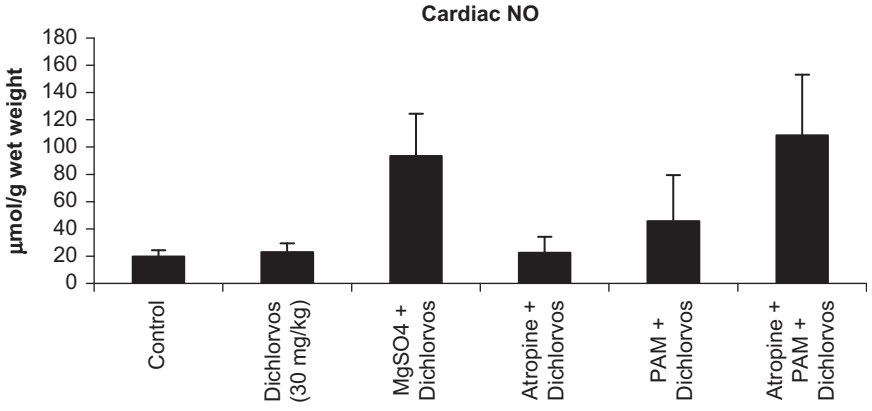

Fig. 1. Cardiac tissue NO levels for the groups.

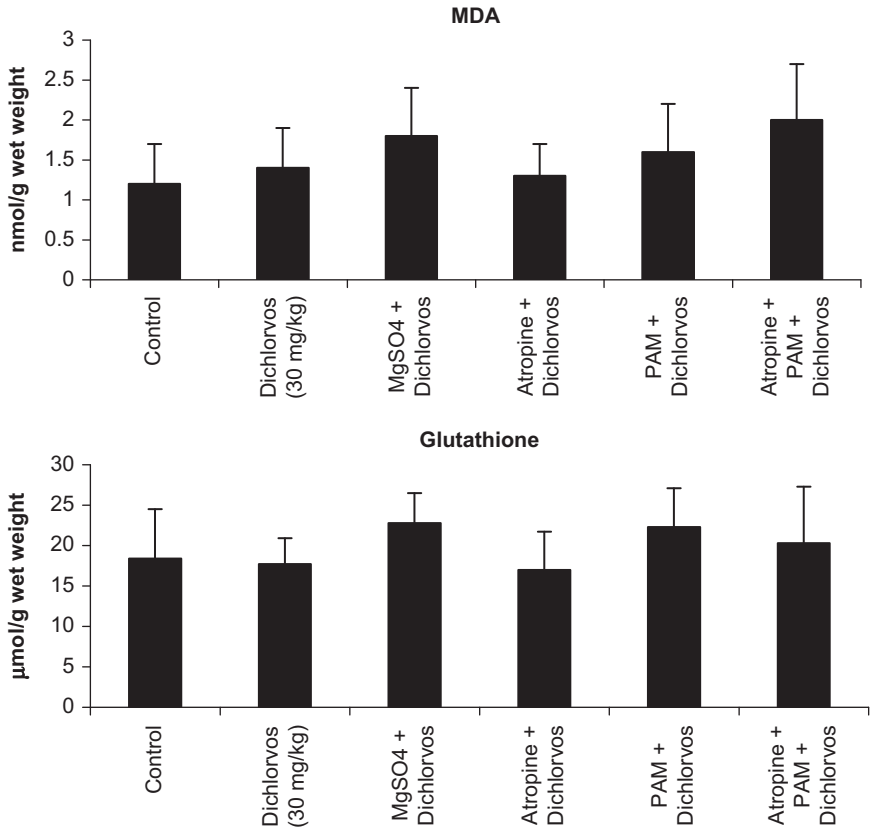

Fig. 2. Cardiac tissue glutathione and MDA levels for the groups.

neuron connection strengths known as synaptic weights are used to store the knowledge [19].

Neural network operates like a "black box" model, and does not require detailed information about the system. Instead, it learns the relationship between the input parameters and the controlled and uncontrolled variables by studying previously recorded data, in a similar way that a non-linear regression might be performed. Another advantage of using ANNs is their ability to handle large and complex systems with many interrelated parameters. They simply ignore excess input data that are of minimal significance and concentrate instead on the more important inputs [14].

A neural network is composed of large numbers of highly interconnected processing elements known as neurons. Fig. 3 shows the basic elements of an artificial neuron. Artificial neuron consists of weight, bias and activation function mainly. The basic features of the network usually consist of an input layer, some hidden layers and an output layer. The simplest form of an each single neuron is connected to other neurons of a previous layer through adaptable synaptic weights. Knowledge is usually stored as a set of connection weights. The output of any neuron is given by:

$$u_i = \sum_{j=1}^{n} w_{ij}x_j + b_i \tag{1}$$

The summation u_i is transformed as the output using sigmoid function as follows:

$$y_j = f(u_i) \tag{2}$$

A back propagation algorithm which is the most widely used training algorithm for the multi layer perception is used in this

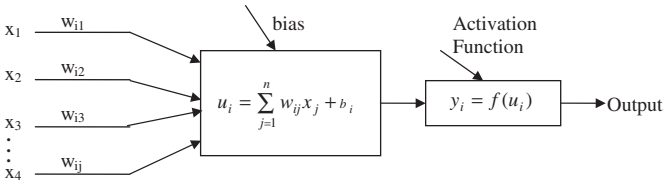

Fig. 3. Basic elements of an artificial neuron.

study because of its applicability and simplicity. It is based on generalized delta rule and was popularized by Rumelhart et al. [20].

The criterions used for measuring the network performance are the correlation coefficient (R), mean squared error and mean absolute percentage error. The correlation coefficient assesses the strength of the relationship between the predicted and experimental results, and it is defined as [21]

$$R(a,p) = \frac{\mathrm{cov}(a,p)}{\sqrt{\mathrm{cov}(a,a)\mathrm{cov}(p,p)}} \tag{3}$$

where $\mathrm{cov}(a,p)$ is covariance between a and p sets that refer to the actual output and predicted output sets, respectively, and given by [21]

$$\mathrm{cov}(a,p) = E\lfloor(a-\mu_a)(p-\mu_p)\rfloor \tag{4}$$

where E is the expected value, μ_a is the mean value of a set and μ_p is the mean value of p set. Likewise, $\mathrm{cov}(a,a)$ and $\mathrm{cov}(p,p)$ are the

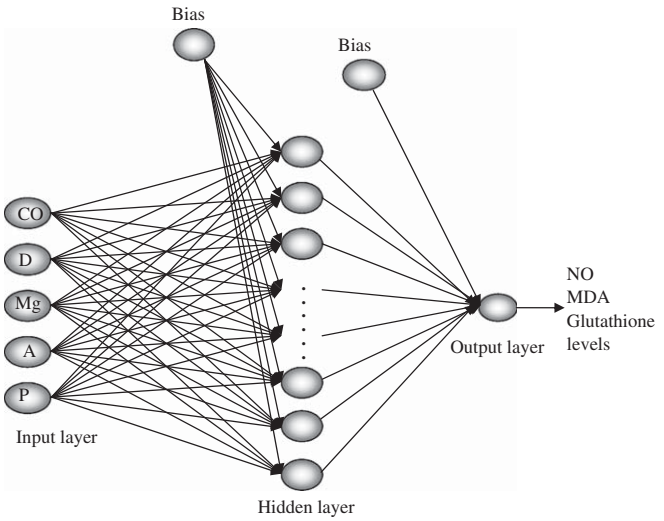

Fig. 4. The architecture of the NN.

auto covariances of a and p sets, correspondingly, and given by

$$\mathrm{cov}(a,a) = E\lfloor (a-\mu_a)^2 \rfloor \quad (5)$$

$$\mathrm{cov}(p,p) = E\lfloor (p-\mu_p)^2 \rfloor \quad (6)$$

The correlation coefficient ranges between -1 and $+1$. R values closer to $+1$ indicate a stronger positive linear relationship, while R values closer to -1 indicate a stronger negative relationship.

The mean squared error (MSE) that determine network performance is formulated as follows

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(a_i - p_i)^2 \quad (7)$$

Finally, the mean absolute percentage error (MAPE) is obtained from

$$MAPE = \frac{1}{N}\sum_{i=1}^{N}\left(\left|\frac{a_i - p_i}{a_i}\right|\right)100 \quad (8)$$

where N is the number of the points in the data set.

4. Modeling with the artificial neural network

The architecture of the ANN model developed in this study is schematically shown in Fig. 4; network consisting of an input layer, a hidden layer and an output layer. Information from the outside environment is received by the input layer neurons, which transmit them to the hidden layer neuron without performing any calculation. The hidden layer neurons then process the incoming information and extract useful features to reconstruct the mapping from the input space. Weights fully interconnected to the neighboring layers. Lastly, the output layer neurons produce the network prediction to the outside world [22].

The selection of a network architecture and parameter settings play an important role in the performance of a NN model. Various network architectures have been investigated aiming at finding the one that could result in the best overall performance. The architecture, from those tested, that gives the best results is shown descriptively in Fig. 5. This architecture has one hidden slab employing the sigmoid activation function. The input slab

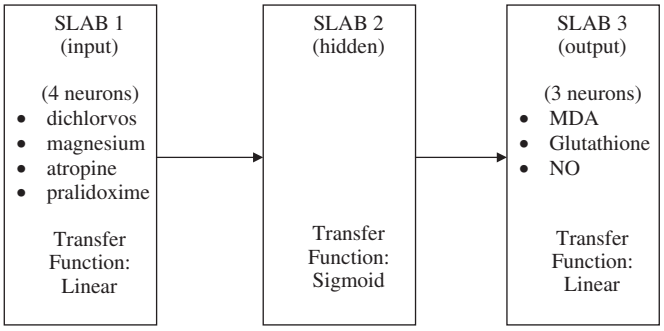

Fig. 5. Neural network architecture with activation function employed.

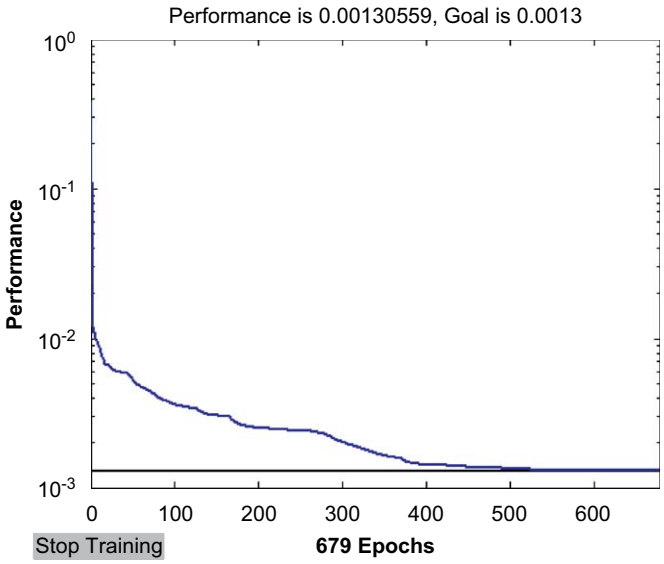

Fig. 6. Variation of mean square error performance with training epochs for the MDA level.

activation function was linear, and the activation in the output slab was also linear.

In this study, the Matlab is used for NN applications. To train and test a neural network, input data and corresponding target values are necessary. The main aim of this study is to formulate and model the effects of some drugs on NO, MDA and glutathione levels in cardiac tissue in acute organophosphate poisoning in rats by the application of neural network based on experimental results. In the model, the experimental results set includes 50 values, of which 38 values were used for training the network and 12 values were selected randomly to test the performance of the trained network.

In the present study, the optimal NN architecture was obtained by trying different number of hidden layers and neurons. The trial started one hidden layer with five neurons. The goal is to maximize correlation coefficient to obtain a network with the best generalization. Many different network models were tried and their R values are calculated. The highest correlation coefficient for NO, MDA and glutathione levels were obtained at a network. Based on this analysis, the optimal ANN architecture was found to be 4-7-1 NN architecture for MDA level, 4-8-1 NN architecture for glutathione level and 4-9-1 NN architecture for NO level with hyperbolic Log sigmoid transfer function (logsig). The best training algorithm used in the study

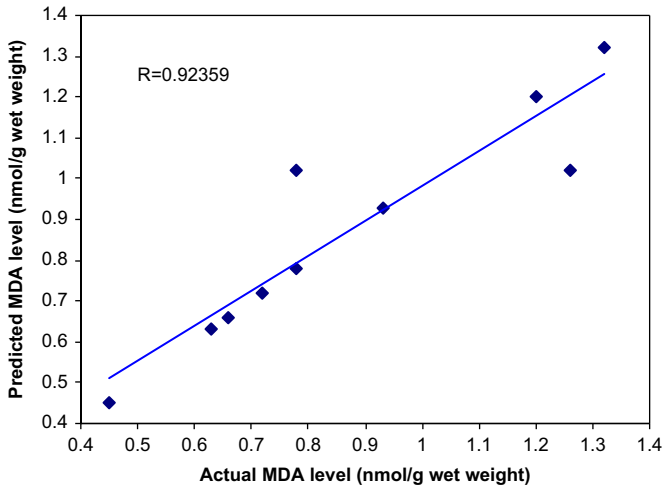

Fig. 7. Comparison of actual and ANN predicted values of MDA level for the test data set.

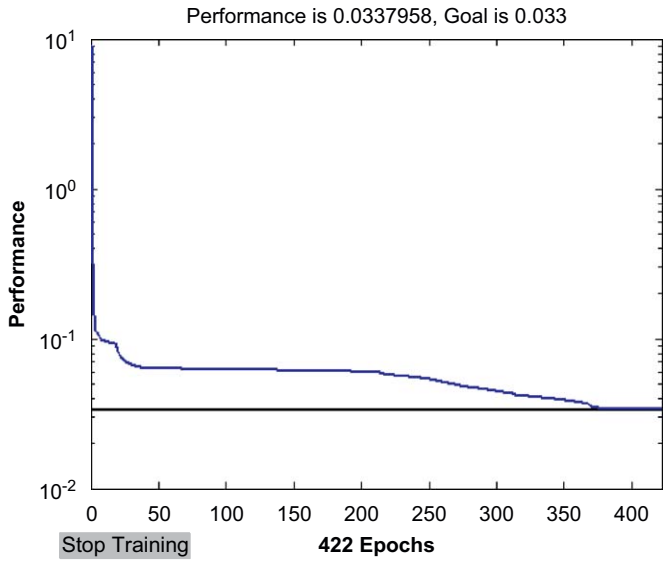

Fig. 8. Variation of mean square error performance with training epochs for the glutathione level.

is the Levenberg–Marquardt (LM) back propagation training algorithm.

5. Analysis results

The ANN model developed in this study is used to formulate and model the effects of atropine, pralidoxime and magnesium sulfate on NO, MDA and glutathione levels in cardiac tissue in acute organophosphate poisoning in rats. A total of 38 samples were used for training the network and other 12 (randomly) were used as a test set.

The optimal ANN architecture was found to be 4-7-1 NN architecture for MDA level. The decrease of the mean square error performance during the training process of this topology is shown in Fig. 6. The regression curve of the output variable (MDA level) for the test data set is shown in Fig. 7.

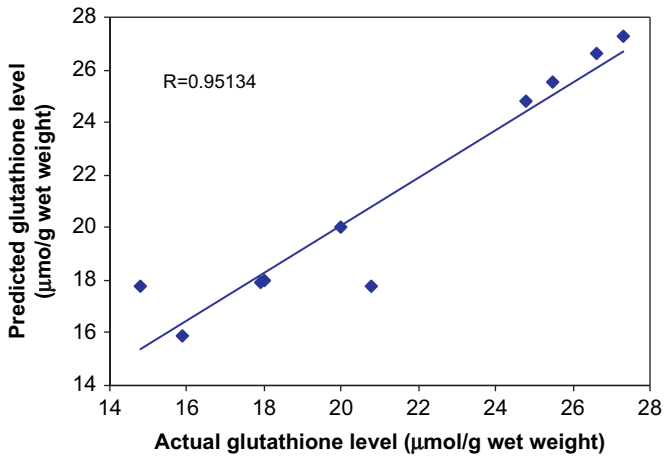

Fig. 9. Comparison of actual and ANN predicted values of glutathione level for the test data set.

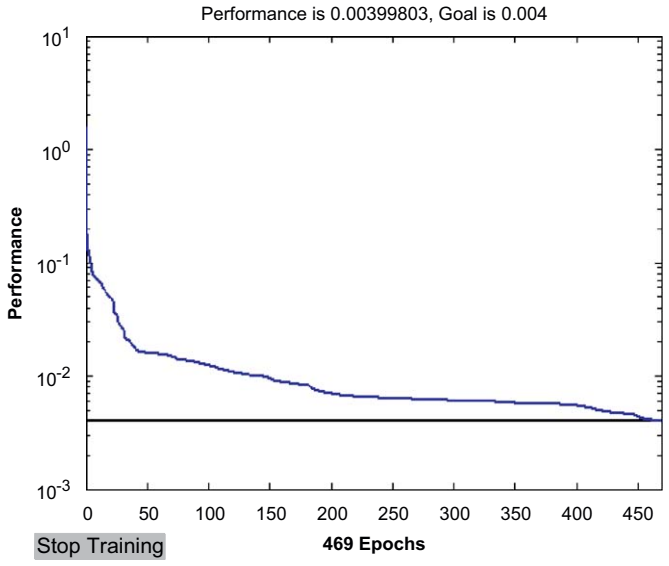

Fig. 10. Variation of mean square error performance with training epochs for the NO level.

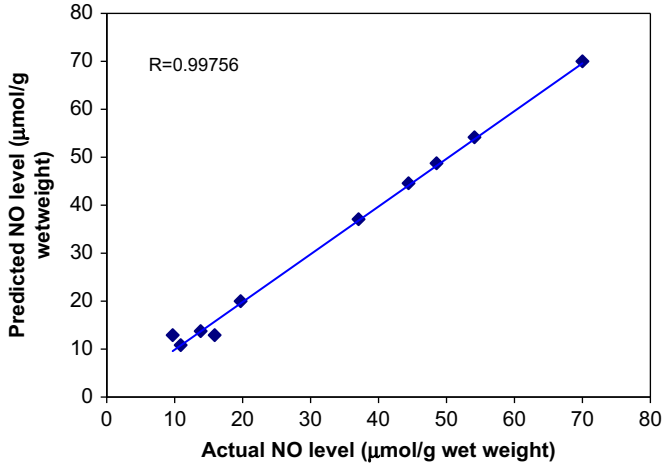

Fig. 11. Comparison of actual and ANN predicted values of NO level for the test data set.

Table 2
Statistical parameters of train and test sets.

		MSE	MAPE	Correlation coefficient R
Malondialdehyde (MDA)	Test set	0.0047	4.9817	0.92359
	Train set	0.0013	3.0755	0.97689
Glutathione	Test set	0.018	3.4693	0.95134
	Train set	0.0338	3.7454	0.91809
NO	Test set	0.0022	5.2624	0.99756
	Train set	0.0039	3.7699	0.99393

The optimal ANN architecture was found to be 4-8-1 NN architecture for glutathione level. The decrease of the mean square error performance during the training process of this topology is shown in Fig. 8. The regression curve of the output variable (glutathione level) for the test data set is shown in Fig. 9.

The optimal ANN architecture was found to be 4-9-1 NN architecture for NO level. The decrease of the mean square error performance during the training process of this topology is shown in Fig. 10. The regression curve of the output variable (NO level) for the test data set is shown in Fig. 11.

The training was stopped when the minimum average error of the training data set was equal to 0.001305 for MDA, 0.0337 for glutathione and 0.00399 for NO level. This is considered good value, enabling the network to give good predictions and avoiding overtraining.

Capability was achieved for both training and testing data sets of MDA, glutathione and NO level. Therefore, the ANN appears to have a high generalization capability. The statistical parameters of testing and training sets of NN models are presented in Table 2. As seen in Table 2, a high correlation coefficient (R) and a low mean absolute percentage error (MAPE) were obtained for the training and testing data sets for MDA, glutathione and NO level. The proposed ANN model for MDA, glutathione and NO prediction had correlation coefficients of 0.97689, 0.91809 and 0.99393, respectively, for training data sets, 0.92359, 0.95134 and 0.91809, respectively, for testing data sets. Moreover, MAPE of the MDA prediction was about 3.0755 and 4.9817 for the training and testing set, respectively. MAPE of the glutathione prediction was about 3.7454 and 3.4693 for the training and testing set, respectively. Similarly, MAPE of the NO prediction was about 3.7699 and 5.2624 for the training and testing set, respectively. As it is seen these MAPE are fairly reasonable. Figs. 7, 9 and 11 also demonstrated that the ANN was quite successful in learning the relationship between the different input parameters and the outputs (MDA, glutathione and NO level). The result of testing phase in Figs. 7, 9 and 11 showed that the ANN was capable of generalizing between input variables and output reasonably well.

6. Explicit formulation

Neural network operates like black-box model. But, this study opens this black box model and introduces the NN application in an explicit formulation. The main objective of this study is to obtain the explicit formulation of MDA, glutathione and NO levels related to the trained NN parameters which are weights and biases. Explicit formulation of proposed NN model as a function of dichlorvos (D—ml), magnesium (Mg—ml), atropine (A—ml) and pralidoxime (P—ml) is obtained.

The explicit formula is obtained using the weights of the trained network given as follows:

$$Net_j = \sum_{i=1}^{n} w_{ij}x_i + b_j \tag{9}$$

where Net_j is the weighted sum of the jth neuron for the input received from the preceding layer with n neurons, w_{ij} is the weight between the jth neuron and the ith neuron in the preceding layer and x_i is the output of the ith neuron in the preceding layer. The output of the jth neuron out_j is calculated with a sigmoid function as follows:

$$out_j = f(Net_j) = \frac{1}{1+\exp(-kNet_j)} \tag{10}$$

where k is a constant used to control the slope of the semi-linear region.

The inputs D, Mg, A and P should be first normalized by 0.44, 0.48, 0.77 and 0.47, respectively, and then enter to the equations shown below. The outputs MDA, Glutathione and NO in the NN model are also normalized by 1.56, 10 and 30, respectively. Trained NN model by using weights and biases, MDA level can be given as follows:

$$MDA = \frac{1.56}{1+e^{(-(34.2735/1+e^{-B1})+(13.2593/1+e^{-B2})+(20.5775/1+e^{-B3})+(26.9474/1+e^{-B4})+(6.3939/1+e^{-B5})+(12.3882/1+e^{-B6})+(25.9053/1+e^{-B7})-27.5566)}} \tag{11}$$

where

$$\begin{aligned}
B1 &= -30.1*D+3.6487*Mg+8.0162*A-3.1444*P+21.0287\\
B2 &= -117.9265*D+27.797*Mg+26.7979*A+4.8197*P+26.9434\\
B3 &= 48.341*D-41.1475*Mg-36.3159*A-34.631*P+5.6085\\
B4 &= -30.9452*D+11.9753*Mg+10.3475*A-23.549*P+13.0771\\
B5 &= -18.7958*D-3.2318*Mg-13.1099*A+49.9313*P-9.1305\\
B6 &= 61.658*D+15.251*Mg+1.6467*A+23.7494*P-25.6961\\
B7 &= 12.1925*D-6.8541*Mg+0.0298*A+7.0788*P-3.5892
\end{aligned} \tag{12}$$

And, the glutathione level can be given as follows:

$$Glutathione = \frac{10}{1+e^{((28.4219/1+e^{-B1})-(10.6551/1+e^{-B2})-(17.1549/1+e^{-B3})-(55.4524/1+e^{-B4})+(9.1156/1+e^{-B5})-(2.2825/1+e^{-B6})-(46.7221/1+e^{-B7})+(55.5946/1+e^{-B8})+2.0998)}} \quad (13)$$

where

$$B1 = -26.1123*D+9.2617*Mg+6.9735*A-8.9651*P+6.2367$$
$$B2 = 49.935*D+4.4417*Mg+46.6958*A-3.7938*P-53.6983$$
$$B3 = -78.5997*D-40.8511*Mg-25.3527*A-9.967*P+37.4305$$
$$B4 = -60.5069*D-3.1149*Mg+13.5773*A+48.839*P-11.0795$$
$$B5 = 33.09*D-3.4313*Mg-9.7922*A+0.3071*P+2.878$$
$$B6 = -29.7151*D+19.1057*Mg-0.4482*A-36.3687*P+21.6141$$
$$B7 = 47.6083*D-74.2407*Mg-48.5378*A-22.278*P+17.5999$$
$$B8 = 61.6618*D-59.7348*Mg-39.1744*A+6.3217*P+2.7195 \quad (14)$$

Similarly, the NO level can be given as follows:

$$NO = \frac{30}{1+e^{((19.9467/1+e^{-B1})+(16.6878/1+e^{-B2})+(22.0636/1+e^{-B3})-(24.315/1+e^{-B4})+(10.4129/1+e^{-B5})+(19.7274/1+e^{-B6})-(23.0842/1+e^{-B7})+(22.5265/1+e^{-B8})-(0.9716/1+e^{-B9})-26.3567)}} \quad (15)$$

where

$$B1 = 30.3525*D+23.4496*Mg-10.9387*A+38.7087*P-21.9314$$
$$B2 = -60.2744*D-9.0984*Mg+2.8714*A+12.114*P+23.7564$$
$$B3 = 72.2916*D-17.992*Mg-13.5145*A-18.861*P-17.5245$$
$$B4 = 113.942*D-13.9899*Mg-6.8641*A-15.5336*P-36.2088$$
$$B5 = 11.0972*D-3.2869*Mg-31.7999*A+14.017*P+6.9455$$
$$B6 = 48.4948*D-3.7774*Mg+6.5583*A+7.2637*P-18.9625$$
$$B7 = -45.344*D+1.4491*Mg-10.3105*A+74.4576*P-19.1644$$
$$B8 = -65.3209*D+26.0168*Mg-4.3526*A+23.5978*P+3.3544$$
$$B9 = -15.1799*D+12.4133*Mg+2.9289*A+13.6756*P-7.1521 \quad (16)$$

It should be noted that the proposed explicit formulation of the NN model presented above is valid for the ranges of training set.

7. Conclusion

In this study, the effects of some drugs on cardiac tissue levels of NO, MDA and glutathione in acute organophosphate poisoning in rats were formulated and modeled by the application of neural network based on experimental results. The proposed ANN models have quite high accuracies where the correlation coefficient (R) found to be quite high 0.97689, 0.91809 and 0.99393 for train sets of MDA, glutathione and NO levels, respectively. As a result of this study, to formulate and model NO, MDA and glutathione levels in cardiac tissue ANN can be effectively used due to ANN have a convenient and inexpensive tool and promising method for modeling the complex relationship especially where no valid model exist. Furthermore the proposed NN models have been used without waste of animal.

Conflict of interest statement

There is no conflict of interest.

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Necla Togun received the degree in mechanical engineering from the University of Gaziantep, Gaziantep, Turkey, in 2001, the M.Sc. degree in engineering from the University of Gaziantep, Gaziantep, Turkey, in 2004. He is currently working towards the Ph.D. degree in the field of artificial neural network applied to internal combustion engine modeling.

Since 2002, he had been a Researcher assistant at the University of Gaziantep, Gaziantep, Turkey.