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Transformation of a Nomogram for Drug-induced QT-Prolongation to a Computerized Neural Network

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ABSTRACT

Drug-induced prolongation of the QT interval of the electrocardiogram is well recognized as a risk for increased mortality. A nomogram relating QT-interval to heart rate has been previously developed to assess this risk. Since other risk factors may be operative, a computerized neural network was derived from the nomogram. The value of such a neural network includes the subsequent identification of factors that may modify the risk associated with cardiotoxic drug therapy, providing an additional predictive tool that may be used to reduce this risk.

Keywords: Neural Networks, Nomogram, QT-Prolongation

Abbreviations: NNA (neural network analysis), ANN (artificial neural network)

INTRODUCTION

Drugs which increase the QT interval of the electrocardiogram may increase mortality during therapy. Among the cardiac events associated with the QT-interval increase is the onset of Torsade de Pointes [1]. While several risk factors may increase QT-interval cardiotoxicity, heart rate plays an important role. A careful examination of the relationship between QT-prolongation and heart rate relative to adverse cardiac events has led to the development of a clinically useful nomogram [2]. As noted in Figure 1, the risk of an adverse cardiac event increases dramatically when the QT-interval and heart rate exceeds the indicated threshold line [3]. While QT-interval and heart rate can be readily assessed, other factors must be considered, since many elevations above the nomogram threshold are not consistently lethal. Other methods must be considered to evaluate and use these additional factors to predictively avoid cardiotoxic events. Among these is computerized neural network analysis (NNA). NNA is somewhat analogous to signal processing through a series of biological neurons, which generate output from a multitude of input signals. In data analysis with NNA software, a wide variety of input factors can be used to model outcomes (output), resulting in predictive utility [4]. For the purpose of the present application, QT-interval and heart rate were used as independent input variables, with no increase or increase in cardiotoxic risk as the dependent output variable. This simple neural network can be used as a template to be expanded by other investigators to assess additional risk factors, with the potential to predictively avoid cardiotoxic events.

MATERIALS AND METHODS

For the design of this neural network, the software package NeuralTools 7 was obtained from Palisade Corporation (Ithaca, New York). This program uses Microsoft Excel (Redmond, WA) as the interface for data entry and analysis. The two input variables were QT-interval and heart rate, each arranged as columns in Microsoft Excel. The corresponding output for each QT-interval and heart rate value pair was obtained from the nomogram ("NO" for no increased risk and "YES" for increased risk) and arranged in the output variable column. In this manner, each row in the Excel datasheet is a point obtained from the nomogram. One

hundred forty points from the nomogram threshold line were assigned to the "NO" output category. An equal number of points distributed above and below the threshold line were selected and entered into Excel, with output category assignments of "YES" and "NO", respectively (Figure 2). This threshold format for output designation was previously used for the design of an ANN from an acetaminophen toxicity nomogram [5]. NeuralTools 7 was used to train and test a network on this dataset of 520 data points.

RESULTS AND DISCUSSION

New input data values not associated with this dataset were used to assess the ability of the ANN (artificial neural network) to predict the appropriate output category when compared to that of the nomogram (Figure 3). The predictive value of the ANN improves with a larger dataset and an increase in point density in the dataset near the threshold line relative to high or low QT-interval values. This is important, since points very close to the threshold line are highly prone to prediction error. For the points selected, the predictive output appears to match the result that one would reasonably obtain from visual inspection of the nomogram. While transformation of the nomogram to a computerized neural network alone offers no advantage, the ability to use this network design to expand input data variables to more accurately predict outcomes offers a significant clinical advantage. Since points above the nomogram threshold line may identify an eminent cardiotoxic event, interventions must likewise be prompt. In addition to QT-interval and heart rate, it is well known that drug interactions that increase the blood level of drugs prolonging the QT-interval have deleterious consequences [6]. In addition, impaired renal function may increase blood levels of drugs associated with QT-prolongation. These and other factors can be readily introduced as inputs into a modified neural network and used to expand the utility of the network, especially for improving clinical outcomes.

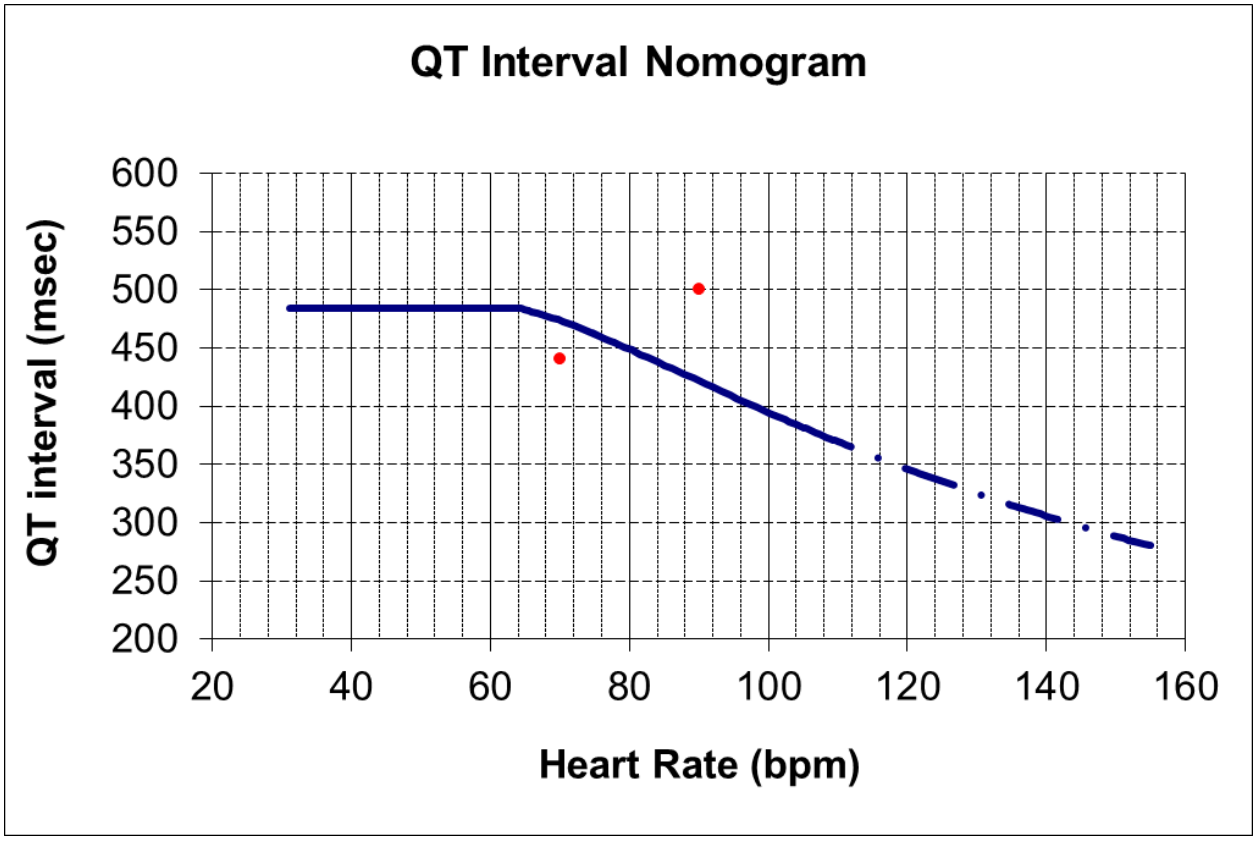

Figure 1. QT Interval Nomogram. Combinations of QT interval and heart rate above the line have an increased incidence of cardiotoxicity, including Torsade de Points (adapted from WikiTox, [3]).

HR	QT Interval	RISK
40	350	NO
40	300	NO
40	250	NO
60	450	NO
60	400	NO
60	350	NO
60	300	NO
60	250	NO
80	400	NO
80	350	NO
80	300	NO
80	250	NO

HR	QT Interval	RISK
100	350	NO
100	300	NO
100	250	NO
120	300	NO
120	250	NO
140	250	NO
40	500	YES
40	550	YES
60	500	YES
60	550	YES
80	475	YES
80	500	YES
80	550	YES
100	450	YES
100	500	YES
100	550	YES
120	400	YES
120	450	YES

Figure 2. Sample points from the nomogram arranged as a dataset in Excel. HR indicates heart rate, QT-interval as measured from the electrocardiogram and corresponding risk RISK of cardiotoxicity.

HR	QT-Interval	RISK	Nomogram Threshold Line
70	450	NO	BELOW
80	480	YES	ABOVE
90	405	NO	BELOW
100	415	YES	ABOVE

Figure 3. RISK predictions relative to nomogram. Input values (HR and QT-Interval) not in the dataset were used to test RISK predictions by NNA. Note the corresponding position in the nomogram.

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