Chapter 4.16
Clinical Decision Support System to Prevent Toxicity in Patients Treated with Digoxin

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ABSTRACT

Digoxin (DGX) is drug used to control signs and symptoms involved in congestive heart failure and atrial fibrillation. Due to its narrow therapeutic range more than 10% of the patients treated with DGX can suffer toxic effects, but it is estimated that half of the cases of digitalis toxicity could be prevented. Two multivariate models were developed to prevent digitalis toxicity, with data of 125 patients monitored at the Pharmacy Service of the University Hospital Dr. Peset (Valencia, Spain). One hundred and six patients were used to develop the models and the other (55) to validate them. The logistic regression model achieved a 90.9% of sensitivity and 81.8% of specificity in the validation set with only 2 variables that are statistical significant (cardiomegaly and digoxin plasmatic concentration). The feed-forward multilayer network model achieved 100% of sensitivity and 90.9% of specificity equal in the validation set but all 14 variables studied are used as input

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in this model. A software for identifying patients at risk in order to implement preventive measures to avoid signs and symptoms of digitalis toxicity was developed.

INTRODUCTION

Digoxin is one of the most widely prescribed drugs for the treatment of congestive heart failure and atrial arrhythmia. Despite current guidelines relegate digoxin use to patients that remain symptomatic after receiving optimum doses of antihypertensive and the utility of digoxin in atrial dysrhythmia is only superior to other agents when the patient has associated heart failure.

Digoxin use has decreased significantly from 31.4% (late 2001) to 23.5% in (late 2004) ($p<0.00001$), the number of toxic or potentially toxic exposures to digoxin requiring hospitalization has not decreased (Hussain, Swindle, & Hauptman, 2006), specially in geriatric patients who uses about 80% of the global consumption of digitalis drugs (Kernan, Castellsague, Perlman, & Ostfeld, 1994; Warren, McBean, Hass, & Babish, 1994).

The Institute for Safe Medication Practices classifies digoxin as a "high alert medication"; that is drugs that bear a heightened risk of causing significant patient harm when they are used in error (*High-alert medication list.*).

Therefore, digoxin intoxication represents about a fourth of the adverse drug events (ADEs) detected in the geriatric population, which frequently results in hospitalization (Gurwitz et al., 2000). Digoxin is the fourth drug class (7.7%) most frequently involved in potentially preventable adverse drug events at the emergency room (Otero et al., 2006), and one of the ten drugs most frequently associated with medication that demand interdisciplinary (physicians, pharmacists and nurses) actions (Llopis, Albert, Sancho, Calipienso, & Jiménez-Torres, 1999; Markota, Markota, Tomic, & Zelenika, 2009; Mutnick et al., 1997; Rupawala, Kshirsagar, & Gogtay, 2009).

The wide pharmacokinetic and pharmacodynamic variability of digoxin due to its narrow therapeutic range, together with the multiple factors that can affect the organism response to digoxin and the diversity of clinical manifestations of digitalis toxicity (DT), results in digoxin being frequently associated to drug related problems. It is estimated that half of the cases of DT could have been prevented; this gives an opportunity to improve the treatment that patients receive and reduce medical costs (Gandhi, Vlasses, Morton, & Bauman, 1997).

In order to improve efficiency, with the available resources, it is necessary to identify those patients that are most susceptible to profit from pharmaceutical care actions; that is to say, to identify patients with either potential or real drug related problems, in order to prevent the former and resolve the latter. Multivariate statistical methods, as logistic regression and neural networks, are useful tools to develop prediction models of morbidity (toxicity or therapeutic failure) associated to drug use, particularly when factors that influence the therapeutic response are analyzed.

Neural networks technology does not require "a priori" models and represents an important improvement to the multivariate analysis. Artificial neural networks stand out for being able to find complex relations between dependent variables and the independent ones, in agreement with their superior ability to discover non linear relations, a representative characteristic of pharmacologic variability. The application of these models presents advantages over the actual statistical methods, although this doesn't mean not to recognize their limitations (Soria, Jiménez, & Serrano, 2000).

Neural Networks in Clinical Medicine

Artificial neural networks have been applied with marked success in classification problems, modelling, signal processing and time series prediction in