Digoxin: the Results of the DIG Study in the XXI Century

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Abstract

After the report that there was no statistical significance in the general mortality of the DIG study, the indication of digoxin in the treatment regimens for congestive heart failure (CHF) drastically decreased. *Post hoc* studies that reassessed the DIG study data, indicated that an aspect that was not considered in this multicenter study has a critical influence on the prognosis of patients: the serum levels of digoxin. Regarding those that received a placebo, the general mortality and hospitalization were decreased in patients with a digoxin level < 0.9 ng/ml. At the first study that assessed the influence of digitalis in an experimental model of CHF, we verified in our lab that female rats with congestive syndrome secondary to myocardial infarction have a prolonged survival when undergoing treatment with digitoxin.

The current information recommends that the merits of digoxin continue to be analyzed in order to adequately establish its importance in the treatment of CHF.

Key words

Cardiac glycosides; cardiotonic agents; digoxin; heart failure.

Recent data indicate that in the USA, more than 5 million individuals present Congestive Heart Failure (CHF) and, each year, 550,000 new cases are diagnosed, resulting in approximately one million hospitalizations, with direct and indirect costs estimated at 29 billion dollars/year, e with a mortality rate varying from 5% to 75% a year[1]. Apparently, essathis amount is common in Western countries [2]. Such data confer a relative importance when seeking a medication for CHF that have as its main characteristics: improvement in the quality of life, economic viability, easy administration, absence of important adverse effects, easy to combine with other medications and, mainly, improve patient survival.

After the description by a William Withering of the virtues of the derivatives of *Digitalis lanata* in the treatment of patients with hydropsy in the XVIII century, the several small studies carried out until the end of the XX century were not considered enough to define the merits of the use of digitalis in patients with heart failure. In 1993, two randomized, double-blind and placebo-controlled studies were published, which analyzed the clinical influence of the withdrawal of digoxin in patients that had been receiving the medication: PROVED[3] and RADIANCE[4]. The patients followed at the PROVED trial received a diuretic associated to digoxin and the patients followed at the RADIANCE study received digoxin associated with diuretic and angiotensin-converting enzyme inhibitor. After the period of stabilization, the digitalis was substituted by placebo in one of the groups of each of these trials. In the two studies, weeks after the digoxin withdrawal, there was a decrease in exercise tolerance, decreased ejection fraction (EF), increased heart rate and decompensation in the group of patients that had digoxin withdrawn. These results characterized the clinical benefit of the use of digitalis.

In 1997, the *Digitalis Investigation Group* (DIG)[5] study was published, which was designed to analyze whether the suse of digitalis reduced mortality and hospitalization due to CHF. The DIG randomized, between 2 groups, 7,788 patients that maintained sinus rhythm, used diuretics and angiotensin-converting enzyme inhibitor (ACEI): those who received digoxin and those who received placebo. The main arm of the study followed 6,800 patients with EF < 45%. Although the digoxin decreased the number of hospitalizations, the difference identified between the mortalities due to CHF exacerbation reached borderline values, but did not attain statistical significance.

After these data were reported, the use of digitalis in the treatment regimens for CHF clearly decreased, even though there is documented evidence that: 1) the digitalis are the only oral inotropic agents that do not increase mortality in chronic CHF[6]; 2) they constitute a class of medications which, when used at appropriate doses, do not cause hypotension, electrolytic alterations and renal adverse effects[2]; the mortality and hospitalization due to all causes were reduced at the *post hoc* analysis of the US Carvedilol[7]; 4) the benefit of spironolactone was significant only for the patients that received digoxin in the RALES study[8]; 5) the joint analysis of the data from the PROVED and the RADIANCE studies showed that the patients who received digoxin associated to diuretic and ACEI presented a better evolution than those who received only the last two drugs[9].

After the report of the results of the DIG study, there was a marked decrease in the use of digitalis in the treatment of heart failure at the end of the last century and the first years of the XXI century. The OPTMIZE–HF (*Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure*) registry[10] reported that only 30% of the patients with systolic ventricular dysfunction were receiving treatment with digoxin before the admission and the digoxin was added or maintained after the discharge in only 8% of them.

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This change in the use of digoxin seems to be predominantly due to the lack of statistical significance at the analysis of mortality described in the DIG study. Probably, there was also a contribution from the study that questioned the safety of digoxin use in female patients[11]. Finally, the availability of new neurohormonal antagonists, such as beta-blockers and angiotensin II and aldosterone antagonists, the lack of financial support from the industry for digitalis and the sophisticated devices used for cardiac resynchronization might have contributed to decrease the use of digoxin in CHF.

In the most recent American guideline[1], considering that the effect of digoxin on survival has not been statistically characterized, the use of digitalis went from class IA to IIA indication; however, in the Canadian guideline[2], the recommendation for the use of this medication is categorized as class IA in symptomatic patients that have already received ACEI and beta-blockers.

Posterior analyses of the data from the DIG study proposed new interpretations for the results of the trial. The analysis of the subgroups indicated that digoxin decreases the mortality in certain situations. Several authors have indicated that the plasma levels of digoxin – an aspect that was not considered in the DIG study – is a critical determinant of the results[12-18]. One of the studies[12] demonstrated that patients with plasma digoxin levels between 0.5 and 0.9 presented a decrease in mortality and hospitalization rates. Higher serum levels of the digitalis decreased hospitalization, but did not alter the mortality due to all causes. Considering patients with a mean serum level of 0.89 ng/ml, Rich et al[13] verified that the digoxin had beneficial effects on mortality and hospitalization in all age groups studied in the DIG study. Ahmed[14] described a decrease in mortality and hospitalization in elderly individuals who received daily doses ≤ 0.125 mg/day.

Contrary to the widespread opinion that the female sex is more susceptible to the toxic effects of digitalis, Adams et al[15] demonstrated that the question is more complex. There is a linear association between the serum levels of digoxin and mortality in the women from the DIG study; those that had serum levels between 0.5 and 0.9 ng/ml presented lower rates of morbidity and did not present exacerbation of mortality. The women with plasma levels > 1.2 ng/ml presented a decrease in survival. Ahmed et al[16] compared the data from the DIG patients that stopped receiving digoxin with those who continued to receive it. They verified that the patients who continue to receive the medication presented a decrease in mortality and hospitalization rates.

Analyzing the data of the male patients included in the DIG study, Rathore et al[17] described that those with serum levels between 0.5 and 0.8 ng/ml presented a significant decrease in mortality; levels between 0.9 and 1.1 ng/ml were not associated with differences when compared to the patients receiving placebo and those with serum levels > 1.2 ng/ml presented a higher mortality rate than those receiving placebo. In another publication, Ahmed et al[18], evaluating the data of patients from the DIG study that received ACEI and diuretics, verified that the digoxin decreased mortality and hospitalization rates during the first year of follow-up.

Our study, considering the current evidence, suggests that a new clinical trial be carried out, with the objective of evaluating the influence of low doses of digoxin on mortality.

Additionally, there are consistent indications that, among the beneficial effects of the drug in CHF, in addition to its positive inotropic action, the digitalis also promote modulations of the sympathetic nervous and renin-angiotensin-aldosterone systems[19-21], and that these neurohumoral effects are attained with low plasma levels of digitalis[22].

It is indisputable, however, that it is very difficult to repeat another clinical trial to test the efficacy of digitalis on the decrease of mortality in humans and this fact confers importance to experimental studies that evaluate this question. Moreover, some particularities are included in the large clinical trials, when studying the survival of large population samples, which can make it difficult to perform the evaluations.

Special difficulties are created by the diversity of the series regarding the age ranges, the type, intensity and evolution of the pathology, the degree of myocardial dysfunction and the association with other diseases and medications. The lack of such inconveniences in animal studies, which allow a stricter control of intervening factors, highlights the merit of experimental studies.

Several studies have analyzed the influence of therapeutic regimens on the survival of animals with heart failure secondary to the occlusion of the coronary artery. Angiotensin-converting enzyme antagonistsic[23-25], AT1 receptor antagonists[24], neutral endopeptidase antagonists[25,26], endothelin antagonists[27,28] and calcium antagonists[29], among others, have been tested experimentally and represent an important contribution for clinical practice. A special highlight is for the pioneering study that described the beneficial effect of captopril on the survival of infarcted female rats and which disclosed the importance of angiotensin-converting enzyme blockers in cardiologic practice[24].

No studies in the literature had tested the influence of the treatment with digitalis on the survival of animals with heart failure. In our laboratory, we analyzed the influence of digitoxin on the survival of female rats with congestive heart failure secondary to myocardial infarction. The corresponding text is to bewas published at the Journal of Cardiac Failure[30].

Briefly, female rats with large infarctions, that had ingested digitoxin at previously standardized doses of 0.1 mg/kg of weight/day[31], and that were followed for 280 days, presented: 1) prolonged survival; 2) attenuation of myocardial dysfunction and 3) attenuation of pulmonary congestion, when compared to other female rats that did not receive digitalis.

Considering the special characteristics of the investigation, these data must not be considered as a challenge against the existing analyses in humans, but must call the attention toward the need for the assessment of special situations, to which the conclusion of absence of digitalis influence on the survival of patients with heart failure might not be appliedapply.

The report of studies following the DIG study, which analyzed the data from patients that were part of this large trial, created quite a discussion about the concept that the digoxin does not prolong survival of cardiopathic patients with HF. The way toward the final elucidation of this question has yet to be defined. It is possible to consider that the strategies to be followed are uncertain and one cannot define the

time required for such final elucidation to be achieved. Unfortunately, it is reasonable to consider that, as many other questions, these can also be forgotten and that an adequately established definition of the role of digitalis in the treatment of HF might not occur.

Nevertheless, there are reasons to regret that the digitalis are being marginalized without an irrefutable definition that they are unnecessary in the routine treatment of HF. There is enough documentation demonstrating its efficiency at low doses, as it does not jeopardizeaffect survival, does not add comorbidities, decrease the activities of the sympathetic nervous system and the renin-angiotensin-axis, whereas it improves the physical capacity and well-being and does not trigger any significant drug interaction, being a class of medication that can be prescribed to populations with low socioeconomic levels and which is easy to control by oral administration.

The adequate role of the digitalis in the treatment of heart failure is yet to be defined by Cardiology in the XXI century.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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