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Is there a role for digoxin in atrial fibrillation without heart failure?

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Abstract

Digoxin remains one of the most frequently prescribed drugs in the management of atrial fibrillation. The main indications for digoxin in atrial fibrillation are restoration of sinus rhythm, prevention of recurrence and slowing of the ventricular rate. However, none of these effects of digoxin have been confirmed in placebo controlled studies. In addition, recent reports suggest increased mortality in patients with atrial fibrillation without heart failure taking digoxin. The aim of this article is to review the role of digoxin in atrial fibrillation without heart failure. (Cardiol J 2009; 16, 5: 483–486)

Key words: atrial fibrillation, digoxin, increased mortality, cardioversion

Introduction

Digitalis has been used for more than two centuries. Its beneficial effect in atrial fibrillation (AF) was probably first recognized by Withering [1]: "It (digitalis) has a power over the motion of the heart, to a degree yet unobserved." Indications for digitalis in AF without congestive heart failure are: restoration of sinus rhythm, prevention of recurrence, better rate control and shorter durations of AF paroxysms [2].

Despite these effects not being confirmed, digitalis is one of the most frequently prescribed drugs in AF [3–7]. In the SPOFITT study [7], 53% of patients were taking digoxin (D). Furthermore, D is considered a relatively safe drug despite its narrow therapeutic toxic ratio. This assumption, however, was recently challenged by reports suggesting that D has adverse effects on survival in patients with higher than 1.2 ng/mL serum D concentration (SDC) [6] and in those with AF without heart failure [6–10]. The aim of this review is to discuss the role of D in AF in patients with preserved left ventricular function.

Electrophysiological effect of digoxin on the atria

Digitalis, similarly to AF, shortens the atrial effective refractory period (ERP) also known as electrical remodeling [11–16]. In an experimental model of AF, delayed recovery of atrial electric remodeling after D was reported by Tieleman et al. [13] while Sticherling et al. [14] found similar results in humans. According to these authors [14], shortening of atrial ERP was more pronounced with secondary episodes of AF more common in digitalized patients compared to controls. Furthermore, Tieleman et al. [15] reported a higher, though not statistically significant, incidence of recurrence of AF after cardioversion in patients taking D. This suggests that D is associated with a higher rate of recurrence of AF and could be the first step in the development of chronic AF [11, 16].

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Role of digitalis in restoration of sinus rhythm

Until a few decades ago, the role of digitalis in AF was mostly based on clinical experience and some experimental results. Friedberg [17] suggested that conversion of AF by digitalis is "purely coincidental." Pick [18] believed that D has an antiarrhythmic effect in AF. According to Hurst [19], improved hemodynamics and ventricular rate slowing are the most likely mechanisms for restoration of sinus rhythm. Finally, according to Schamroth [20], digitalis has a pro-fibrillatory effect.

Weiner et al. [21] evaluated the effect of D on conversion of new onset AF (< 14 days) for 47 episodes in 45 patients. Patients received 1.5 mg of D intravenously over 12 hours and were followed up to 96 hours. Sinus rhythm was restored in 85% of AF episodes. The main limitations of Weiner's report are the lack of a control group and concomitant use of additional drugs. In addition to lone AF, patients included in this study had ischemic heart disease, hypertension and valvular heart disease.

Falk et al. [3] reported the first placebo control study in 36 patients with AF < 7 days without heart failure, acute ischemic process, electrolyte imbalance or severe renal impairment. Digoxin was administered orally 1.4 mg in divided doses at 0, 4, 8 and 14 hours, respectively, or until conversion. Restoration of sinus rhythm occurred in eight patients (44%) in the placebo group and in nine (50%) patients taking D. There was no significant difference between the two groups.

Jordaens et al. [4] reported similar results ten years later. These authors administered 1.25 mg of D over the course of eight hours to 19 patients, while 20 patients received a placebo. The two groups were matched for age, gender, body weight, underlying heart disease, initial heart rate and duration of AF. Digoxin and placebo restored sinus rhythm within 12 hours in 43.6% and 47.4%, respectively, without significant difference in the ventricular rate before or after cardioversion.

In the DAAF trial [5], 239 patients with recent onset AF were divided into two groups: 122 received a placebo and 117 D. The average D dose was 0.88 mg. Restoration of sinus rhythm in the D and placebo group was 51% and 46% respectively (not significant).

The main difference between the DAAF and the two previous studies was the D effect on ventricular rate. In the DAAF study, D users had significantly slower ventricular rate as early as two hours after initiation of therapy, persisting up to 16 hours. The reason for different D effect on ventricular rate is not clear. One possible explanation is the role of the autonomic nervous system. For example, in patients with high sympathetic tone at the onset of AF, D may be less effective in controlling the ventricular rate [22].

Finally, Murgatroyd et al. [23] reported a double blind placebo controlled study of D's effect in patients with paroxysmal AF. The end point was time interval to two symptomatic episodes of AF, using the patient's activated event recorder. There were 43 patients divided into two groups. The median time interval before two transmitted AF episodes in the D and control group was 18.7 days and 13.5 days respectively ($p < 0.05$). Time to the first episode of symptomatic AF was also longer in D users. As in the DAAF study [5], the heart rate was lower in patients taking D (128 bpm) than in the control group (138 bpm; $p < 0.01$). As the authors pointed out, the most likely reason for the delay of symptomatic AF was slower rate rather than restoration of sinus rhythm.

Adverse effects of digoxin

Increased mortality in patients after acute myocardial infarction taking D was suggested in the early 1980s based on post hoc analysis [24, 25]. More recently, Spargias et al. [26] found D as an independent predictor of increased total mortality (hazard ratio of 1.41 and $p = 0.014$) in patients with heart failure after myocardial infarction.

Similarly, in the DIG [27] patients taking D had a higher cardiac death rate in comparison to those in the placebo group ($p = 0.04$). According to Gheorghiade and Pitt [28], cardiac arrhythmias without worsening heart failure and coronary artery disease are probably the main causes of increased cardiac mortality in the DIG study.

Higher mortality of subjects taking D was also reported by Casiglia et al. [10] in a population study of 2,254 patients aged over 65. The patients included in this study were followed for 12 years and divided into two groups. In the first group were 1,977 patients in sinus rhythm without heart failure. In the second were 187 patients with heart failure and 90 patients with AF.

Patients in the first group who were taking D had a higher 12-year mortality than untreated ones (58% *vs*. 49.5%; $p < 0.0001$). The cardiovascular mortality was also higher in patients taking D (21.5% *vs*. 17.7%; $p < 0.0001$). In patients with heart failure, the survival rate was similar in both groups, and in those with AF, mortality due to heart failure was higher in patients taking D (28.1 *vs*. 4.2%; $p = 0.02$).

The adverse effect of D is also seen in patients with AF. In the AFFIRM sub-study [8], patients taking D had a higher mortality than non-digitalized ones (hazard ratio 1.42). According to the authors, the lower survival rate in patients taking D was more likely due to an increased risk of death, rather than an adverse D effect [8]. However, the authors also suggested that "there may be other measured or unmeasured variables that influence physicians to choose digoxin."

Hallberg et al. [9] compared one-year mortality in three groups of patients after discharge from coronary care units in Sweden. In the first group were patients with AF without heart failure; the second were those with congestive heart failure; and the third group were patients with AF and congestive heart failure.

The main finding of Hallberg's study was increased mortality in D users without heart failure (hazard ratio 1.42). No adverse effect of D was seen in patients with or without AF and heart failure. Among important limitations of this study were: SDC was not available, probably not all confounders could be included, and there was no information on renal and left ventricular function. Probably more important was the post-discharge management. For example, did all patients continue to take D, how many were treated with beta-blockers, antiarrhythmic drugs and what was the rate of sinus rhythm restoration?

Gjesdal et al. [7] analyzed mortality of D users and non-users in the SPORTIF III and V study, which compared warfarin with a direct thrombin inhibitor ximelagatran. In this report, of 7,329 patients, 53.4% were taking D. The mortality was 6.5% in D users and 4.1% in non-users ($p < 0.001$; hazard ratio of 1.58).

After risk factor adjustment, increased mortality was still significantly higher in digitalized patients ($p < 0.001$; hazard ratio 1.53). Patients taking D had a higher incidence of fatal myocardial infarction (8.6% *vs*. 5.7%; $p = 0.026$), sudden cardiac death and heart failure. Despite being a planned sub-study before its closure, this study has certain limitations. Most likely some confounded risk factors could not be included in the analysis. Also, the indications for D, mechanism of heart failure and SDC were unknown.

What are the possible explanations for increased mortality in patients with AF taking D? One explanation is that D has a narrow therapeutic/ /toxic ratio. Therefore a pro-arrhythmic effect has to be considered. This, however, seems unlikely because digitalis toxicity usually causes symptoms, and patients included in studies are closely followed.

A second explanation is that digitalized patients have a higher incidence of fatal myocardial infarction and 'other vascular death' suggesting intravascular thrombosis as the cause of increased mortality. This explanation is supported by recent studies, according to which not only AF but also D induces platelets' and endothelial cells' activation [28, 29]. The role of platelets and endothelial cell activation in intravascular thrombosis is well known.

Finally, it is important to point out that the adverse effects of D are based on univariate and multivariate analysis and/or on retrospective studies instead of prospective randomized ones. Because of a lack of commercial support, a randomized study confirming adverse D is unlikely.

An alternative practical approach is to replace D with more effective pharmacological and non--pharmacological therapies such as electric cardioversion, ibutilide or pill in the pocket (flecainide or propafenone). To achieve these goals, the medical community has to become more familiar, not only with the limited efficacy of D in AF without heart failure, but also with its possible adverse effects.

Conclusions

We reviewed the role of D in patients with AF without congestive heart failure. According to placebo controlled studies, D has no role in cardioversion or recurrence prevention of AF. The efficacy of D in patients with paroxysmal AF as an atrioventricular nodal blocking agent is not completely clear. Some studies suggest better ventricular rate control, others failed to confirm atrioventricular nodal blocking D effect.

An important recent finding is the adverse effect of D in patients with AF and normal left ventricular function. The best approach to confirm this unfavorable D effect on survival would be a randomized study. As we have said, this is unlikely due to a lack of commercial support. We believe that for patients with AF and normal left ventricular function, the best practical recommendation is to replace D with more effective therapies for cardioversion and prevention of recurrence and rate control.

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