SCIENTIFIC EDITORIAL

Digoxin therapy: A persisting interest despite contrary winds

Traitement par digoxine : un intérêt persistant malgré des vents contraires !

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Abstract Digoxin therapy is used to treat heart failure patients for more than 200 years. However, absence of effect on overall mortality found in the DIG study associated with frequent adverse effects due to overdosing in elderly patients with impaired renal function finally persuaded medical opinion to the weak interest of digoxin in chronic heart failure. Its image of old-fashioned drug in the mind of young cardiology generations appears widely distorted, and suffers from the absence of promotion by pharmaceutical industry, given a very low cost and a rapid arrival onto the generic market. Yet, regarding strict data from the literature, it remains a lot of positive factors in favor of the interest for digoxin: reduction of morbidity, reduction of mortality at low serum concentration < 1.0 ng/ml, very low cost with favorable cost-effectiveness ratio. This article challenges some arguments for defending digoxin as another first-line therapy as well as ACE inhibitors and beta-blockers in the treatment of chronic heart failure.

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MOTS CLÉS
Digoxine ; Insuffisance cardiaque ; Morbi-mortalité ; Bloqueurs du système rénine-angiotensine ; Coût de la santé

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
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What is the question?

Digitalis glycosides were among the first cardiovascular therapeutic agents to be used in medicine. Digoxin, obtained from the leaves of *Digitalis lanata*, is the most common preparation of digitalis, and has been used to treat heart failure patients for more than 200 years. However, digoxin acquired a negative image at the end of the 1980s, as a result of clinical trials testing new oral inotropic agents, in which high mortality rates were linked to this class of cardiovascular agent. Consecutively, the pathophysiological concept of heart failure was changed from a haemodynamic model to a neurohormonal model with the advent of the era of angiotensin-converting enzyme (ACE) inhibitors [1], which resulted in digoxin being positioned in a secondary role in the therapeutic management of heart failure. Absence of effect on overall mortality in the DIG study [2], associated with frequent adverse effects due to overdosing in elderly patients with impaired renal function, finally diminished medical interest in the use of digoxin in chronic heart failure. Data from heart failure registries and clinical trials show a considerable fall in digoxin use from approximately 80% to less than 30% in the past 10 years [3]. Yet, if the actual data from the literature are considered, there are many positive factors to support digoxin use. The opinion held by younger cardiologists of digoxin as an old-fashioned drug appears to be widely misplaced, and the drug suffers from the absence of promotion by the pharmaceutical industry, given its very low cost and rapid arrival onto the generic market. What we now need to know is whether the effectiveness of digoxin is underestimated, and whether it could represent an interesting therapeutic alternative that is worthy of reconsideration in the treatment of patients with chronic heart failure.

What can we expect from digoxin?

Digoxin has shown numerous favourable effects over many years [4,5]. It improves clinical symptoms, exercise capacity, and cardiac haemodynamics at rest and at exercise by decreasing left ventricular filling pressures and pulmonary capillary wedge pressure, increasing cardiac output and slowing heart rate. It also exerts favourable neurohormonal effects by enhancing parasympathetic tone and reducing increased plasma levels of norepinephrine, aldosterone and renin activity, each of which is stimulated in heart failure. All these effects enable digoxin to improve renal function.

Previous digoxin discontinuation trials, PROVED [6] and RADIANCE [7], showed an indirect favourable effect of digoxin, in that withdrawal in patients with heart failure receiving the drug chronically in association with ACE inhibitors led to an increase in worsening heart failure and mortality. The DIG study [2], published in 1997 and performed in more than 6700 patients with systolic heart failure, did not show any effect on overall mortality; however, there was a highly significant, positive effect on the combined endpoint of heart failure mortality and hospitalization for heart failure (25% reduction), mainly due to a substantial 28% reduction in hospitalization for heart failure. Nevertheless, complementary analyses highlighted an increase in presumed arrhythmic deaths [2] and an excess in overall mortality in women, without any convincing explanation [8].

In order to better understand why these contradictory negative effects of digoxin on mortality and major positive effects on morbidity exist, post-hoc analyses were performed using digoxin serum concentrations from patients included in the DIG trial. It appeared that digoxin improved left ventricular ejection fraction (LVEF) below serum concentrations of 1.2 ng/mL, but that the effect disappeared above this threshold [9]. Again, digoxin withdrawal caused a decrease in LVEF, associated with an increase in cardiovascular events. All-cause mortality was reduced significantly (by 23%) when serum digoxin concentrations in 30-day survivors were between 0.5 and 0.9 ng/mL, and this was always accompanied by a very clear reduction in morbidity (38% relative reduction in the need for heart failure hospitalization), which was also seen at serum concentrations between 1.0 and 1.5 ng/mL [10,11]. No interaction between digoxin and gender was noticed [12], thereby suggesting that earlier results showing increased mortality in women [8] was perhaps a spurious result due to residual confounding from serum concentrations.

Recently, some studies were published concerning the effects of digoxin in heart failure [13,14], which did not show any improvement in mortality-morbidity criteria after prescription of digoxin. However, these studies were single centre and retrospective, without presupervised and randomized groups. When serum concentrations were measured [14], the median serum digoxin concentration was 0.75 ng/mL, ranging from a first quartile of 0.50 ng/mL to a fourth quartile of 1.40 ng/mL for a median daily drug dosage of 0.130 mg/day. As established by DIG post-hoc analyses, these values appeared to be too high—at least for 25–33% of the study patients. Some criticisms of these studies were made in a recent editorial [15]: for instance, the inclusion of younger patients with more severe heart failure (in terms of New York Heart Association [NYHA] class) than would usually be included in large randomized trials, such as the DIG trial.

The case for prescribing digoxin

European guidelines for the treatment of heart failure, revised in 2008 [16], recommend prescription of digoxin in patients with symptomatic heart failure and atrial fibrillation (Class IC), and in patients in sinus rhythm with symptomatic heart failure and LVEF < 40% (Class IIa, level of evidence B). When looking at the evolution of digoxin recommendations over time, we see that the guidelines were inconsistent from 2001 (no recommendation for patients in sinus rhythm) to 2005 (recommendation for patients in sinus rhythm, Class IIa, level of evidence A), and finally to 2008 (same recommendation but Class IIa, level of evidence B), despite no new data having published; this illustrates the large variability in opinion and interpretation of the literature by the experts. The recommended treatment algorithm proposed for patients with symptomatic heart failure and reduced LVEF ranks digoxin among treatments of third intention after angiotensin receptor blockers (ARBs) and aldosterone antagonists if the QRS width is less than or equal
to 120 ms; if the QRS width is greater than 120 ms, resynchronization therapy is preferred [16]. Yet, the arguments for prescribing digoxin or any blockers of the renin-angiotensin system other than ACE inhibitors are not very different.

Digoxin has a neutral effect on mortality but improves the combined endpoint of morbimortality in patients in NYHA class II—IV heart failure with LVEF less than or equal to 45%. The efficacy of digoxin was established in a unique, large, randomized, controlled trial that included more than 6700 patients [2]. The proof of efficacy for ARBs and aldosterone blockers in heart failure is not really superior to that for digoxin.

A role for aldosterone antagonists was identified as a result of the RALES study [17], which showed a reduction in overall mortality in patients in severe NYHA class III—IV heart failure with LVEF less than or equal to 35%. It is well known that drug efficacy is often easier to demonstrate in patients with severe disease than in those with mild to moderate disease. Moreover, patients in the RALES study received a rather low dose of ACE inhibitors (63 mg/day for captopril, 15 mg/day for enalapril or 14 mg/day for lisinopril). In addition, in a subgroup analysis of the RALES trial involving patients who were in the spironolactone group, the benefit was not statistically significant in those who did not receive digoxin or ACE inhibitors. Nevertheless, the efficacy of aldosterone antagonists was confirmed by the results of a second study (the EPHEBUS trial), which tested eplerenone [18]. However, the patient profile was totally different (patients with left ventricular systolic dysfunction in the acute phase of myocardial infarction), and a post-hoc analysis showed clearly that the favourable effect on morbimortality attributed to eplerenone was only present when the drug was initiated between the third and seventh days after acute myocardial infarction; a later prescription had no significant effect at all on outcomes [19].

Proof of efficacy of ARBs in association with ACE inhibitors also came from a unique study — the CHARM-Added trial [20]. The efficacy of candesartan was expressed in terms of morbimortality criteria. As with digoxin in the DIG trial, no positive effect was found on overall mortality. Moreover, the efficacy of other ARBs (losartan, valsartan) in association with ACE inhibitors is questionable, and the triple association of an ACE inhibitor, ARB and beta-blocker was shown to have a deleterious effect in the Val-HeFT trial [21]. Digoxin thus stands comparison with these other competitors.

Digoxin therapy has another major argument in its favour: a low price with an extremely positive cost-effectiveness ratio. According to the DIG trial, the treatment of only 11 patients for 3 years should be sufficient to avoid one costly hospitalization for heart failure (total cost: around €1000). By comparison, it is necessary to treat 70 patients for 4 years with an ACE inhibitor to avoid one non-fatal myocardial infarction (total cost: €60,000—90,000 depending on the ACE inhibitor used) [22]. Previous analyses from the PROVED and RADIANCE trials showed that the use of digoxin in patients with stable heart failure would result in net annual savings of $406 million, with a 90% range of probability of $106—822 million [23].

Conclusions

Digoxin is an effective drug for patients with heart failure, and should be used as a first-line therapy in association with ACE inhibitors and beta-blockers for patients with clinical heart failure and left ventricular dysfunction, with LVEF less than or equal to 45%. The drug has a large morbidity benefit, certainly at least as large as that seen for ACE inhibitors in heart failure, and should not be ignored by prescribers. Moreover, the large randomized heart failure trials that showed the benefits of ACE inhibitors, beta-blockers, ARBs and resynchronization therapy were generally performed with background digoxin therapy (up to 75% of the patients in the RALES trial!). Other trials would be useful to confirm the post-hoc analyses of the DIG trial. However, it probably is a vain wish, unless institutional funding can be found, given how neglected the marketing of the drug is. Digoxin’s rank on the scale of chronic heart failure therapy appears to be underestimated and it deserves to be reconsidered at a suggested dosage of less than or equal to 0.125 mg/day given immediately to attain a serum digoxin concentration of less than 1.0 ng/mL. The risk of adverse effects would thus be reduced dramatically, while a major gain would be achieved in terms of public health. Digoxin might also be reconsidered in the therapeutic management of acute decompensated heart failure [24]. Let us hope that in the near future, government agencies do not decide to sideline digoxin in the cardiovascular pharmacopoeia on the pretext of its age and so-called weak efficacy!

Conflict of interest statement

The authors declare no conflict of interest.

References


