



## **Digoxin: The Medicine from Hell?**

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**By Hans R. Larsen MSc ChE**

Despite incontrovertible evidence that digoxin (Lanoxin, digitalis, Digitek) should never be prescribed for **lone** atrial fibrillation some cardiologists still do so. Thus, I decided to update my 2002 article.

Please feel free to share this article with anyone who might be interested, including your physician. The truth about the dangers of digoxin needs to be spread far and wide.

Digoxin, originally derived from the foxglove plant, has been in use for over 200 years as a heart medication. The drug raises the intracellular  $\text{Ca}^{2+}$  concentration resulting in an increase in the force of heart muscle contractions (positive inotropic effect) and a reduction in ventricular heart rate. From its original application digoxin has expanded into the treatment of atrial fibrillation and lone atrial fibrillation. Most medical textbooks still laud digoxin as an effective drug for heart failure, but does it actually work?

The Digitalis Investigation Group, a large team of American and Canadian researchers more than 10 years ago presented the findings of a large, randomized, double-blind, placebo-controlled trial of digoxin in the treatment of heart failure patients. The three-year trial involved over 7000 patients with heart failure (left ventricular ejection fraction less than 0.45). The patients were divided randomly into two equal-sized groups with one group receiving 0.250 mg of digoxin per day and the other group receiving a placebo; all patients in both groups continued on ACE inhibitors and diuretics. The average follow-up time was 37 months. At the end of the trial 35% of the participants had died in each group. The death rate attributable to worsening heart failure was slightly less in the digoxin group, but the number of deaths from other cardiovascular events such as arrhythmias and strokes was higher. Patients on digoxin were less likely to be admitted to hospital for worsening heart failure (26.8 versus 34.7% for controls), but had higher admission rates for suspected digoxin toxicity (2.0 versus 0.9%)[1,2]. Digoxin is particularly dangerous for patients over the age of 60 years. In this age group the mortality associated with acute digoxin toxicity is almost 60%[3].

The researchers conclude that digoxin does not reduce the risk of death from heart failure or other causes, but that it does reduce the rate of hospital admissions, especially for worsening

heart failure. In other words, while digoxin may, to some extent, ameliorate the symptoms of heart failure it does not reverse or cure it nor does it reduce the risk of death from this condition[1,2].

British researchers followed 484 heart failure patients for three years and found that the mortality among those taking digoxin was 38.9% as compared to only 21.3% among controls. The researchers conclude that the use of digoxin in heart failure patients is associated with an adverse prognosis and suggest that beta-blockers and spironolactone may be a better choice for ameliorating the symptoms of heart failure[4].

A team of American, Norwegian and Swedish researchers studied 7329 participants in the SPORTIF III and IV trials aimed at comparing the effectiveness of the anticoagulants warfarin (Coumadin) and ximelagatran in afib patients. About 53% of participants were on digoxin throughout the study. The researchers found a higher mortality (6.5%) in the digoxin group than in the group not using digoxin (4.1%). After adjusting for confounding variables, they conclude that digoxin users have a 53% (relative) higher mortality than do non-users. They suggest that in heart failure patients the adverse effects are counterbalanced by the positive inotropic effect, whereas in AF patients, who do not benefit from the inotropic effect, the adverse effects of digoxin dominate and lead to the 53% relative increase in mortality among users[5].

As if the inherent toxicity of digoxin was not enough to curtail its use, there is now also evidence that the drug, even at dosages normally considered safe, can cause visual problems, serious skin rashes, and may significantly aggravate asthma problems[6,7,8].

Of particular concern for women is the recent finding by a team of Danish and American researchers that digoxin increases the risk of breast cancer among postmenopausal women. Their study involved 5,565 women diagnosed with invasive breast cancer during the period 1991 to 2007 and 55,650 matched population controls. The researchers found that the use of digoxin for at least a year was associated with a 30% greater risk of being diagnosed with invasive breast cancer. The association did not change when adjusted for age, hormone replacement therapy, other drugs, medical history (reason for prescribing digoxin), and mammography exposure. The researchers conclude that digoxin treatment increases the risk of invasive breast cancer among postmenopausal women and that this risk increases with increasing duration of treatment[9].

### **Toxicity and Interactions**

The "therapeutic window" for digoxin is very narrow. Most patients are started on a dosage of 0.250 mg/day; however, this is often too little for some patients and too much for others. Very careful evaluation is required in order to find just the right dosage. Unfortunately, this is rarely done in actual practice.

Researchers at the Health Care Department in Maryland found that in the period 1985 through 1991 over 200,000 of 3.3 million digitalis users were hospitalised because of digitalis intoxication. It is ironic that digitalis is often prescribed for people who suffer from atrial fibrillation and yet, the most common manifestation of digitalis intoxication is atrial fibrillation. Other symptoms of digitalis poisoning are nausea, vomiting, diarrhea, psychoses, and fatigue. Perhaps the most disturbing finding in the study is that in 73% of all cases the reason for prescribing the digitalis in the first place was unclear or weak. The researchers also point out that the high level of hospitalisation for adverse effects of digitalis is, to a large extent, due to inadequate monitoring of patients taking the drug. It is also of concern that for the period in

which the researchers uncovered data for the 200,000 hospitalizations only 577 adverse events involving digitalis were reported directly to the FDA by doctors or hospitals[10].

Other researchers have noted that digoxin is often prescribed for seemingly no good reason. Dr. Wilbert Aronow of the Mount Sinai School of Medicine found that 19% of patients admitted to a nursing home had been prescribed digoxin. A thorough medical examination and evaluation concluded that 47% of these patients should not be taking digoxin at all. Dr. Aronow also noted that 18% of the patients receiving digoxin had been misdiagnosed as having congestive heart failure when, in fact, they were suffering from edema or dyspnea (laboured breathing). Digoxin therapy was safely discontinued in the 47% of the patients for whom it had been inappropriately prescribed.[11].

And if that is not enough, digoxin may also cause sinus bradycardia, heart block and ventricular arrhythmias, and interacts with a host of other medications among them amiodarone (Cordarone), flecainide (Tambocor), propafenone (Rythmol), tetracycline, calcium channel blockers, and the herbs Siberian ginseng and St. John's wort[12,13,14].

There is now also evidence that digoxin, when combined with the antidepressant paroxetine (Paxil), can result in severe digitalis toxicity. Japanese physicians recently reported a case of a 68-year-old woman who developed severe digoxin (digitalis) intoxication after starting on paroxetine (Paxil) for depression, insomnia, and difficulty concentrating. The patient had suffered from atrial fibrillation for 2 years and, during this time, had been treated with 0.25 mg digoxin and 1 mg warfarin daily. Two days after beginning on 20 mg/day of paroxetine she experienced nausea, vomiting, and dizziness. Delirium with visual hallucinations followed on day 4 and by day 8 she could no longer eat or walk. On day 9 the doctors suspected digitalis intoxication (serum digitalis concentration was 5.2 ng/mL compared to the normal range of 0.5-2.0 ng/mL). An ECG showed numerous PVCs and complete A-V block. On day 10 all medications were withdrawn resulting in the patient going into bradycardia as a rebound effect of discontinuing digoxin. On day 19 digoxin and warfarin (but not paroxetine) were restarted. The patient remained depressed, developed pneumonia, and died in hospital 3 months later. The physicians speculate that paroxetine and digoxin are metabolized via the same pathway and that the competition leads to digitalis intoxication[15].

### **Digoxin and Atrial Fibrillation**

Almost 20 years ago, Dr. Rodney Falk MD, a leading electrophysiologist at Boston City Hospital made the following statement in an article entitled "Digoxin for Atrial Fibrillation: A Drug Whose Time has Gone?":[16]

*Studies now suggest that in patients with atrial fibrillation, digoxin is a poor drug for controlling heart rate during exertion, has little or no effect in terminating the arrhythmia, and may occasionally aggravate paroxysmal atrial fibrillation.*

Nevertheless, digoxin is still routinely prescribed for patients with atrial fibrillation even though there is no evidence that it is beneficial and ample evidence that it may actually be harmful. Digoxin does not convert atrial fibrillation to sinus rhythm[17,18]. Its ability to slow the heart rate during an atrial fibrillation episode is doubtful[18] and there is no evidence that it prevents future episodes of paroxysmal atrial fibrillation[19,20]. Dr. Rodney Falk again sums it up, "*Digoxin is probably not of value for preventing tachycardia (rapid heart beat) at the onset of paroxysmal atrial fibrillation and its use as sole agent for this indication, although widespread, has no basis*"[20].

Not only is digoxin useless in the prevention and treatment of atrial fibrillation it can actually be detrimental. Dr. Philippe Coumel, MD head of the cardiology section of the Hopital Lariboisiere in Paris says, "*Not only are beta-blockers or digoxin not indicated in vagal atrial fibrillation, but they are definitely contraindicated as they tend to promote the arrhythmia and may block the action of conventional antiarrhythmic treatment*"[21]. Dr. Coumel's statement has been endorsed by the American Heart Association[22].

Researchers at the University of Michigan Medical Center go even further in their condemnation of digoxin. Their conclusion from a recent clinical trial, "The results of the present study suggest that digoxin may facilitate or promote early recurrences of atrial fibrillation after conversion to sinus rhythm not only in patients with vagotonic (vagal) atrial fibrillation, but also among the general population of patients with atrial fibrillation"[23]. It is now also clear that digoxin may not only prolong the duration of episodes, but may actually convert the paroxysmal (intermittent) form to chronic AF[24].

Digoxin also interferes with cardioversion. The 2006 Guideline for the Management of Atrial Fibrillation clearly states, "Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended"[25].

Digoxin is also a problem for persistent afibbers undergoing electrical cardioversion. Researchers at Lund University Hospital in Sweden found that being on digoxin at time of cardioversion was associated with a 2.3-fold increase in risk of relapse into afib. They also noticed that patients on digoxin had significantly longer episodes than did afibbers not on digoxin[26].

Perhaps most disturbing is the recent observation made by Swedish researchers that, although digoxin has been routinely prescribed for AF patients for close to 100 years, its long-term safety has never been evaluated in this patient population. Their recent study involved 21,459 atrial fibrillation patients admitted to a coronary care unit in Sweden during the period 1995 to 2003. The overall mortality in this group was 9.8%/year, but the annual death rate was 42% higher among digoxin users than among those who had not been prescribed digoxin.

All mortality rates were adjusted for about 60 possible confounding variables (other possible risk factors for death). Of particular interest to lone afibbers is the finding that the detrimental effects of digoxin were far worse for relatively healthy patients than for those with multiple risk factors. Thus, AF patients with AF and the least number of other risk factors were more than twice as likely to die within a year after leaving hospital if they had been prescribed digoxin.

The researchers conclude that digoxin is an independent risk factor for death among AF patients placed on long-term therapy with the drug. They also re-emphasize that there is no evidence that digoxin is helpful in speeding up conversion to normal sinus rhythm, or in preventing recurrence of AF episodes[27].

Finally, our own LAF Survey V confirms the inappropriateness of prescribing digoxin for lone afibbers. Twenty-two (12 vagal, 1 adrenergic, 9 mixed) afibbers had tried digoxin. Only 1 mixed afibber had found it useful in keeping heart rate under control. The remaining 21 (95%) had found no benefits from taking the drug. Seventeen (77%) of all users reported side effects with the most common being palpitations and atrial fibrillation (32%) and fatigue (23%). The most common dosage was 0.25 mg daily[28].

Yes, digoxin may truly be the medicine from hell – it certainly should never be used by people with lone AF. If a medicine is needed for control of heart rate, then calcium channel blockers such as verapamil or diltiazem, or beta-blockers like atenolol or metoprolol would be better choices – except for vagal afibbers who should not take beta-blockers.

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1320 Point Street, Victoria, BC, Canada V8S 1A5  
Phone: (250) 384-2524  
E-mail: [editor@afibbers.org](mailto:editor@afibbers.org)  
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