LEADING ARTICLE

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Inappropriate Use of Digoxin in the Elderly

How Widespread is the Problem and How Can it be Solved?

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Abstract

Cardiovascular disease is ubiquitous within the elderly population and requires treatment with multiple types of medications. As with any cardiovascular pharmaceutical regimen, the risk versus the benefit of each medication must be strongly considered. This is particularly true where, for various reasons, adverse effects are more often prevalent and pronounced. Over the years, it has been documented that digoxin is a frequently prescribed medication in elderly populations. Although this drug can be beneficial when used in the appropriate setting, recent data would suggest that inappropriate administration of digoxin is common and not without potentially serious consequences.

Currently, the use of digoxin can be advocated to control heart failure in atrial fibrillation and when added to ACE inhibitors and diuretics in those patients with symptomatic heart failure related to systolic left ventricular disfunction. It is likely that the excessive use of digoxin in elderly populations as discussed in this review is perhaps based on the prevalence of diastolic heart failure in the elderly as well as other co-morbid conditions that may mimic heart failure signs and symptoms. Since the elderly appear to be at high risk for digoxin toxicity, the inappropriate use of this medication to treat these conditions could result in significant and unnecessary morbidity.

It is proposed that echocardiography should be performed in most elderly patients when congestive heart failure is suspected. This simple diagnostic tool, along with a careful history and medical examination, would hopefully prevent the misinterpretation of confusing clinical findings and would help to identify the patients with normal systolic function or valvular disease such as critical aortic stenosis, where digoxin treatment would not be warranted.

If it is necessary to administer digoxin, then the likelihood of significant toxicity can be greatly reduced by using an algorithm to calculate the appropriate dosage, which takes into consideration the patient's gender, bodyweight and creatinine clearance. Although it is probable that the indications for digoxin use to treat congestive heart failure will continue to evolve, at the present time most would recommend using this agent in symptomatic heart failure related to a reduction in left ventricular systolic function or when associated with atrial fibrillation.

The elderly population in developed countries throughout the world is rapidly increasing. Currently, approximately 12% of the population of the US is over 65 years of age, and it is estimated that this may increase to 17% soon after the turn of the century.[1] Due to the often complicated spectrum of chronic diseases common in elderly patients, they are necessarily treated with polypharmacy. There are reports that hospitalised Medicare patients receive an average of 10 prescription drugs and that in the US, nursing homes residents are often given between 4 and 7 drugs daily, many of which are inappropriate or ineffective.[2,3]

Cardiovascular drugs comprise the most frequently used class of pharmacological agents since heart and vascular disease is ubiquitous within the elderly population, representing the greatest cause of morbidity, mortality and hospitalisation. It has been estimated that 40% of the drugs prescribed to the elderly, including diuretics, exhibit specific cardiovascular actions.[1]

A major challenge to clinicians treating the elderly is to administer medications in a judicious manner in order to optimise their efficacy and avoid toxicity. The physiological changes that occur during the aging process, often in association with one or more specific disease states, cause important alterations in the distribution and disposition of many drugs.[1,2] While these agents can also exhibit important toxicities, it is imperative for the treating physician to individualise therapy and develop a firm understanding of the changes in drug selection or administration that may be necessitated by significant alterations in pharmacokinetic and pharmacodynamic profiles. Consideration must also be given to the coexistence and physiological significance of multiple chronic diseases as well as concomitant medications, the potential for drug interactions and compliance of the individual patient.

Because of the high prevalence of congestive heart failure and atrial arrhythmias in elderly individuals, digoxin is one of the most commonly prescribed medications in patients over 65 years of age. This mildly inotropic agent exhibits a narrow therapeutic window, particularly in the elderly, and therefore may account for toxicity and significant morbidity in this population. Furthermore, the manifestation of digoxin toxicity in the elderly may be atypical and thus more difficult to identify than in younger patients.[1,4] The coexistence of one or more other chronic conditions may also complicate and confuse the clinical picture, making it less clear when and how digoxin should be used. Justifiably, there is concern among health care professionals that digoxin therapy is overused, and there are recent data from observational studies identifying inappropriate use of digoxin in the elderly.[5,6] In this review, these issues will be addressed as will the features unique to the elderly population that predispose them to digoxin toxicity. Additionally, the manifestations of digoxin toxicity and approaches that may prevent the inappropriate use of digoxin in elderly patients will be discussed. The trials from which we have extracted most of our current knowledge concerning digoxin therapy will also briefly be reviewed. When interpreting the data from these heart failure clinical studies, consideration must be given to the fact that the elderly are under-represented and therefore extrapolation to clinical practice may be difficult.

1. General Indications for Digoxin Therapy: Lessons from Clinical Trials

Before one can assess the degree to which digoxin may be inappropriately used in elderly patients, one must first review the appropriate indications for therapy as we know them today. There is general acceptance of the concept that digoxin is useful for controlling the ventricular response in supraventricular arrhythmias such as atrial fibrillation. Rather than acting directly, digoxin slows conduction through the atrioventricular node via its parasympathomimetic effects. Other agents such as β-blockers and some calcium antagonists (primarily the first generation agents verapamil and diltiazem) may, however, supplant digoxin since these drugs directly slow atrioventricular conduction and are effective in controlling heart rate both at rest and during periods of catecholamine excess such as during exercise. It is therefore possible to con-

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clude that the role of digoxin in this particular condition is not as important as previously believed and that there are other options available. Digoxin is not effective in preventing the occurrence of atrial arrhythmias and should not be given as prophylaxis for these conditions (i.e. paroxysmal atrial fibrillation).[7,8]

The role of digoxin in treating congestive heart failure has been debated for centuries. Although its utility in treating patients with heart failure and atrial fibrillation is generally accepted, its efficacy in heart failure patients with sinus rhythm has been controversial. This controversy has previously been fuelled by disparate results from small scale studies exhibiting significant design flaws, including small sample size, lack of randomisation, heterogenous populations with vague or mixed heart failure diagnostic criteria, short follow-up intervals and inappropriate cardiac glycoside dosing preparations and administration schedules. Furthermore, the success of ACE inhibitors in alleviating symptoms and prolonging survival in patients with heart failure has raised important questions concerning the added benefit of digoxin. Fortunately, the results from recent, well designed, large scale clinical trials are beginning to provide answers to many of these questions.

Over the past 20 years, several more rigorously designed randomised controlled studies of digoxin in patients with congestive heart failure and normal sinus rhythm have been performed.[9,10] A meta-analysis of 7 studies conducted prior to 1990 involving 617 patients found that overall there was a clinical benefit observed in a small number of patients receiving digoxin. On average, there were no detectable differences in clinical response to digoxin in the majority of patients.[11] Kraus et al.[12] reviewed the results of 13 studies of digoxin in patients with sinus rhythm performed prior to 1993, and concluded that digoxin treatment benefits those with moderate to severe heart failure. Importantly, the authors noted that none of the randomised, placebo-controlled trials that were reviewed identified a negative influence of digoxin therapy on the clinical heart failure parameters tested.

The Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and Randomized Assessment of the Effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) clinical trials were subsequently designed specifically to demonstrate the efficacy and safety of digoxin in patients with normal sinus rhythm and mild to moderate congestive heart failure due to left ventricular systolic dysfunction.[13,14] These studies were designed as companion trials to evaluate the effects of digoxin alone (PROVED) or in combination with ACE inhibitors (RADIANCE). They were both randomised, double-blinded, placebo controlled trials of digoxin withdrawal. Digoxin was administered to achieve target serum concentrations of 0.9 to 2.0 μg/L. In both studies, an average digoxin dose of 0.38mg resulted in 24 hour trough concentration of 1.2 μg/L. Patients withdrawn from digoxin treatment in both studies exhibited clinical deterioration, a reduction in exercise tolerance and worsening cardiac function compared to patients continuing digoxin therapy. Considering both studies, the lowest probability of treatment failure was seen in those patients receiving triple therapy consisting of digoxin, ACE inhibitor and diuretics.

It is important to note that these trials have been criticised because of the limitations inherent in the withdrawal design.[15,16] Since all participants had been maintained on digoxin, a selection bias for better 'responders' may have been introduced. Also, all patients entering the trials had shown that they could tolerate digoxin for at least 3 months without experiencing adverse consequences (i.e. arrhythmia). Some have argued that long term therapy with inotropic agents such as digoxin may accelerate cardiac dysfunction which is manifest only after the agent is withdrawn.[16]

Until recently, the effect of digoxin on heart failure mortality had never been evaluated in a large scale, placebo-controlled, randomised, clinical trial. Patients with heart failure [New York Heart Association (NYHA) class II-III], a left ventricular

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ejection fraction of ≤0.45 (6800 patients) and normal sinus rhythm were enrolled in the multicentre Digitalis Investigator Group (DIG) study.[17] Background therapy included ACE inhibitors and diuretics. The mean age of patients in this trial was approximately 64 years, and 27% of all patients were >70 years old, representing an older cohort than is typically enrolled in heart failure trials. Additionally, there was an ancillary trial whereby 988 patients with heart failure and ejection fractions >0.45 were randomised to receive digoxin therapy or placebo. The dosage of digoxin was determined using an algorithm that considered the patient's age, gender, bodyweight and renal function (table I).[17,18] The results from the DIG trial show that digoxin exhibited a neutral effect with respect to the primary mortality end-point. Those patients randomised to receive digoxin had fewer hospitalisations, and the combined end-point of death or hospitalisation attributable to worsening heart failure was reduced. This finding was true across all subgroups, but the favourable effect of digoxin appeared to be greatest in the sicker patients (NYHA III-IV) with the lowest ejection fractions and in those with radiographic evidence of cardiac enlargement. This finding of a greater beneficial effect in patients with greater functional impairment and cardiomegaly is consistent with previous studies.

Based on these recent studies, the administration of digoxin in combination with ACE inhibitors and diuretics can be considered in patients with significant left ventricular systolic dysfunction and symptomatic heart failure. This is true for all age groups, including the elderly, and is supported by results from the DIG trial which was comprised of older patients representative of the general population of heart failure patients throughout the world.[17]

We routinely administer digoxin to those patients with heart failure and systolic dysfunction who remain symptomatic despite treatment with maximal dosages of ACE inhibitors and diuretics. The role of digoxin treatment in patients with heart failure and relatively preserved systolic function remains controversial and is generally not recommended in the absence of another indication such as atrial arrhythmia. This syndrome of diastolic heart failure with relatively preserved systolic function is common in the older age groups and may be one of the major factors underlying inappropriate digoxin administration in these patients.[19]

2. Inappropriate Use of Digoxin in the Elderly

It is estimated that digoxin is the seventh most commonly prescribed drug in the US and that 20 to

Table I. Digoxin drug administration chart (daily maintenance dose mg/day)[18]

CCC	Bodyweight (kg)					
	50	60	70	80	90	100
10	0.125	0.125	0.125	0.125	0.25	0.25
20	0.125	0.125	0.125	0.25	0.25	0.25
30	0.125	0.125	0.25	0.25	0.25	0.25
40	0.125	0.25	0.25	0.25	0.25	0.25
50	0.125	0.25	0.25	0.25	0.25	0.25
60	0.25	0.25	0.25	0.25	0.25	0.375
70	0.25	0.25	0.25	0.25	0.25	0.375
80	0.25	0.25	0.25	0.25	0.375	0.375
90	0.25	0.25	0.25	0.25	0.375	0.5
100	0.25	0.25	0.25	0.375	0.375	0.5

$$\mathbf{CCC} = \left(\frac{140 - \text{age}}{S_{CR}}\right) X$$

where X = 1 for males and X = 0.85 for females; $\mathbf{S_{CR}}$ = serum creatinine level.

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30% of hospitalised patients are receiving some form of digitalis preparation.[1] Since the incidence of congestive heart failure and atrial tachyarrhythmias, the major indications for digoxin, increase significantly with age, the elderly are commonly prescribed digoxin. Questions have been raised, however, as to the extent with which digoxin treatment is commonly instituted or continued in the absence of appropriate clinical indications.[5,6,20] This is an important issue because of the higher incidence of digoxin toxicity in the elderly and the consequent morbidity and mortality associated with it.[1,2,21] It has been reported that the mortality rate of hospitalised patients with digitalis toxicity is 2.4 times higher than in those without evidence of toxicity.[22] One study has reported that digoxin treatment in the presence of congestive heart failure is associated with an increased number of falls in hospitalised elderly patients.[23]

To gain more insight regarding the incidence and indications for digoxin therapy in an elderly population, Aronow prospectively evaluated 500 consecutive patients admitted to a nursing home who were ≥60 years old (mean age 81 years).[6] Of these, 96 (19%) were receiving digoxin at the time of admission. It was determined that 53% had an appropriate indication for digoxin use (defined as atrial fibrillation and/or heart failure with left ventricular dysfunction) (table II) and 47% were receiving digoxin inappropriately (table III). The majority of patients in the latter group (19%) had been treated for congestive heart failure but exhibited normal left ventricular systolic function. Interestingly, 18% of those inappropriately treated with digoxin had noncardiogenic dyspnoea or oedematous states and had been misdiagnosed with heart failure. Digoxin therapy had been started in 9% of patients because of a history of possible paroxysmal atrial fibrillation.

These findings reported by Aronow[6] are not surprising and are in fact quite predictable when one considers the frequency with which digoxin is prescribed to the elderly population in which the prevalence of heart failure with normal systolic function is high. The incidence of pure diastolic

Table 2 is not available for electronic viewing

dysfunction increases significantly with age and is generally considered a disease of the elderly. In 247 nursing home patients with congestive heart failure (mean age 84 years), Aronow and associates[24] found that left ventricular systolic function was normal in 47% of the patients. This is in contrast to a much lower incidence of normal systolic function (6%) in a group of patients with heart failure who were <60 years old.[25]

The cardiovascular and physiological changes that often occur during the aging process may significantly affect diastolic function.[19,26-29] Primary myocardial changes including left ventricular hypertrophy, increased interstitial fibrosis and in some cases ventricular infiltration with amyloid have been well described during aging and can lead to increased ventricular stiffness with altered diastolic function.[26] Decreased compliance and elasticity of the systemic and coronary vasculature during aging further complicates ventricular hypertrophy and ischaemia.[29,30] Other disorders common in the elderly population (i.e. coronary artery disease

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Table IV. Diseases commonly associated with diastolic dysfunction

Coronary artery disease
Hypertension
Atrial fibrillation
Renal failure
Infiltrative cardiomyopathy
Diabetes mellitus
Restrictive cardiomyopathy

and systemic hypertension) that may complicate diastolic function are listed in table IV.

Although digoxin is presently not recommended for treatment of diastolic dysfunction, the results from the ancillary trial in the DIG study,[17] as discussed in section 1, raise certain questions. In this trial, patients with ejection fractions >45% were randomised to receive digoxin or placebo and, although there was no affect on overall mortality, the combined end-point of death and hospitalisation was improved with digoxin. Importantly, significant adverse effects related to digoxin therapy, as has been reported previously in this patient population, were not observed. One possible hypothesis is that digoxin is potentially beneficial in the elderly patient with heart failure because of its favourable effects on baroreceptor function.[31-33] Certainly, this concept will require further investigation.

According to the Aronow study,[6] digoxin is also commonly prescribed to patients who exhibit some of the signs and symptoms of heart failure but in fact have normal cardiac function. Interestingly, this is not unlike the manner in which digoxin was used 200 years ago when toxicity was very common as the agent was given for many noncardiac oedematous conditions.[34] The clinical diagnosis of heart failure may be difficult to make in the geriatric patient because of concomitant pathological conditions and atypical disease presentations. Exertional dyspnoea is frequently seen in elderly patients who have no evidence of cardiopulmonary disease.[35] Oedema of the lower extremities is a common finding in the elderly and often represents extra cardiac conditions such as venous insufficiency or adverse effects from other pharmacological agents.[35] For these reasons, echocardiography has been advocated as an essential tool for accurately evaluating cardiac disease in the geriatric patient.[36]

Table V. Factors predisposing elderly patients to digoxin toxicity

Decreased lean body mass
Decreased skeletal muscle
Decreased glomerular filtration rate
Potassium deficiency (usually diuretic-induced)
Polypharmacy and drug interactions (e.g. verapamil, quinidine, nifedipine)
Concomitant diseases (e.g. congestive heart failure)

3. Digoxin Toxicity: Predisposing Factors in the Elderly

Multiple factors predispose the elderly to digoxin toxicity (table V). Secondary to changes related to the normal aging process, the pharmacokinetics of digoxin are significantly altered. During aging, there is a gradual reduction in lean body mass and renal function as manifested by a decrease in glomerular filtration rate.[1,37] In that digoxin is a hydrophillic substance excreted by the kidneys, these changes significantly reduce the volume of distribution and excretion of digoxin thus increasing plasma concentrations.[1] Digoxin is avidly bound to skeletal muscle, and the loss of skeletal muscle in the elderly further enhances digoxin plasma concentrations. If heart failure is also present, glomerular filtration rate and lean body mass may be further reduced. It has been estimated that steady-state serum digoxin concentrations in patients on maintenance therapy are double in those patients who are >70 years old compared with younger individuals.[38] However, it is encouraging to note that, when digoxin is administered according to the nomogram used in the DIG trial, toxicity can be significantly reduced.

Other factors predisposing the elderly to toxicity include diuretic-induced potassium deficiency, the frequent use of polypharmacy with the potential for drug interactions increasing digoxin plasma concentrations (table VI) and concomitant diseases such as congestive heart failure which further alter digoxin pharmacokinetics.[1,39]

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One must also be aware of the often atypical presentation of digoxin toxicity in elderly patients. As opposed to younger patients who usually develop nausea and vomiting, the elderly commonly present with anorexia, cognitive changes, hazy vision or arrhythmia.[1,4,40]

4. Recommendations for Digoxin Use in the Elderly

In summary, the addition of digoxin should be considered in elderly patients with heart failure and normal sinus rhythm who remain symptomatic despite receiving treatment with adequate dosages of ACE inhibitors and diuretics. Documentation of systolic dysfunction as the aetiology of heart failure is imperative. It is also appropriate to use digoxin to control the ventricular response to atrial fibrillation, but other medications with less toxicity may be more effective. Digoxin administration in the elderly should be guided by an estimate of creatinine clearance as described previously (table I). The dosage should also be adjusted to account for interactions with concomitant medications that may alter digoxin pharmacokinetics (table VI). Digoxin serum concentrations should be evaluated when there is a change in therapy (i.e. addition of a medication which interacts with digoxin), when renal function significantly changes or when digoxin toxicity is suspected. Normokalaemia should also be maintained.

Based on the prevalence of heart failure related to diastolic dysfunction in the elderly and the multiple comorbid conditions that may mimic heart failure signs and symptoms in older age, it is likely that the inappropriate use of digoxin to treat these conditions is widespread. Considering the fact that the elderly are at highest risk for toxicity, inappropriate use of digoxin in this population may result in significant and unnecessary morbidity. Aronow[36] has proposed that echocardiography should be performed in all elderly patients with congestive heart failure. This approach would help to avoid the misinterpretation of confusing clinical findings and would help to identify the patient with normal systolic function so that digoxin use could be avoided. Furthermore, a complete assessment of valvular function would be possible, enabling identification of the patient with critical aortic stenosis or other valvular abnormalities common in the elderly that may not be recognised on physical examination.

Table VI. Pharmacokinetic interactions with digoxin[39]

Drug	Mechanism of interaction	Change in digoxin serum concentration (%)
Erythromycin	↑ Bioavailability	↑ 50-120
Tetracycline	↑ Bioavailability	↑ 50-120
Phenobarbital (phenobarbitone)	Enzyme induction	↓ 50
Rifampicin (rifampin)	Enzyme induction	↓ 50
Amiodarone	↓ Renal/nonrenal clearance	↑ 70-100
Quinidine	↓ Renal/nonrenal clearance	↑ Up to 100
Diltiazem	↓ Renal clearance (?)	↑ Up to 70
Verapamil	↓ Renal/nonrenal clearance	↑ 70-100
Nicardipine	↓ Renal clearance (?)	↑ 15
Thiazide diuretics	↓ Renal clearance	↑ variable (up to 50)
NSAIDs	↓ Renal clearance	↑ variable (up to 50)
Cyclosporin	↓ Renal clearance	↑ 50-100
Hydralazine	↑ Renal clearance	↓ up to 20
Nitroprusside	↑ Renal clearance	↓ up to 20

NSAIDs = nonsteroidal anti-inflammatory drugs; ↑ = increased; ↓ = decreased.

The potential benefit of this procedure in managing elderly heart failure patients would seem to warrant the cost of echocardiography, at least on a one-time basis. Certainly, the need for continued digoxin therapy should be reassessed during careful medical follow-up and, in situations where the indication for digoxin is poorly documented, further evaluation with thoughtful assessment of the risks and benefits of continuing therapy in the individual patient will be necessary. It is also likely that the potential benefit of digoxin in patients with diastolic dysfunction, as recently suggested by the DIG trial, will continue to be investigated. At the present time, however, most would recommend using digoxin only when left ventricular systolic function is significantly reduced.

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