Use of Digoxin for Heart Failure and Atrial Fibrillation in Elderly Patients

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ABSTRACT

Background: Digoxin has been reported to improve symptoms and reduce hospitalization in patients with heart failure as well as to control rapid ventricular rate in patients with atrial fibrillation. Both of these are high-prevalence diseases in the elderly, and yet studies have indicated that digoxin may not be used appropriately in this population. Clinical trials evaluating digoxin use specifically in the elderly are scarce.

Objective: This article discusses the evidence on the therapeutic use of digoxin in the elderly and the changes in the pharmacokinetics of digoxin with aging to provide recommendations about the appropriate use of this drug in this population.

Methods: Peer-reviewed clinical trials, review articles, and relevant treatment guidelines limited to those evaluating patients aged >65 years were identified from MEDLINE and the Current Contents database (both from 1966 to May 1, 2010) using the search terms *digoxin, pharmacokinetics, heart failure*, and *atrial fibrillation*. Citations from available articles were also reviewed for additional references.

Results: One pharmacokinetic study, 8 clinical trials, and 2 guidelines were identified as relevant to digoxin use specifically in the elderly. In an elderly population (aged ≥65 years; n = 7) compared with a younger population (aged <65 years; n = 6), the elderly had a significant increase in digoxin $t_{1/2}$ (mean [SD]: oral dosing, 69.6 [13.1] vs 36.8 [4.5] hours; IV dosing, 68.8 [12.3] vs 38.2 [3.5] hours; both, $P < 0.05$) and a decrease in total-body clearance (0.8 [0.2] vs 1.7 [0.2] mL/min/kg; $P < 0.05$). The use of digoxin in heart failure has been found to reduce the risk of hospitalization (risk ratio = 0.72; 95% CI, 0.66–0.79; $P < 0.001$). This beneficial effect of digoxin was found to be not significantly different across age groups in those aged >18 years. In terms of atrial fibrillation, the ability of digoxin to control the ventricular rate is believed to be caused by its vagotonic effect on the atrioventricular node. Therefore, digoxin is recommended for ventricular rate control only in patients with heart failure or sedentary lifestyle (ie, low sympathetic tone), or in those who cannot tolerate other rate-control agents. Because the prevalence of heart failure is high among the elderly (15.2 per 1000 population at age 65–74 years, 31.7 per 1000 population at age 75–84 years, and 65.2 per 1000 population at age ≥85 years), many of whom have a relatively sedentary lifestyle, digoxin may be an appropriate agent for ventricular rate control in the elderly.

Conclusions: The elderly population appears to gain comparable benefits as does a younger population from the use of digoxin for heart failure management in terms of symptom improvement and reduction of hospitalization. In atrial fibrillation, digoxin does not control the ventricular rate as efficaciously during exercise and in high adrenergic states as do β-blockers and calcium channel blockers. The elderly have reduced elimination of digoxin, so if digoxin is to be used, the dosing strategy must be conservative and therapeutic monitoring is needed. Further clinical studies are needed to confirm the pharmacokinetic parameters of digoxin in elderly patients with heart failure and/or atrial fibrillation. (*Am J Geriatr Pharmacother*. 2010;8:419–427) © 2010 Elsevier HS Journals, Inc.

Key words: digoxin, geriatrics, heart failure, atrial fibrillation.

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INTRODUCTION

Digoxin is a cardiac glycoside that has been used since the early 20th century to improve symptoms and reduce hospitalization[1] in patients with heart failure with reduced left ventricular ejection fraction (LVEF), as well as to control rapid ventricular rate in patients with atrial fibrillation.[2–5] Both heart failure and atrial fibrillation are highly prevalent diseases in the elderly population (defined, for the purpose of this manuscript, as age >65 years).[6] The risk of heart failure increases from 15.2 per 1000 population in those aged 65 to 74 years, to 31.7 per 1000 population in those aged 75 to 84 years, and to 65.2 per 1000 population for those aged ≥85 years. Similarly, the risk of atrial fibrillation increases with age, from <1% at age <60 years to ~10% at age ≥80 years.

Digoxin is therefore expected to be a commonly prescribed medication in the elderly patient population. A study evaluating digoxin use in 1223 elderly residents of long-term care facilities indicated that 32% of patients with heart failure were prescribed digoxin.[7] In another study evaluating the prevalence of digoxin use in 528 elderly patients in an academic, hospital-based, geriatrics clinic, 17% of the patients were prescribed digoxin. Of these patients, 39% used digoxin for the management of atrial fibrillation.[8] Despite these numbers, few clinical studies have evaluated the therapeutic efficacy or pharmacokinetic/pharmacodynamic parameters of digoxin specifically in an elderly patient population.

Digoxin has a narrow therapeutic index, and toxicity can develop easily if the drug is not dosed and monitored appropriately.[9] In the past decade, the use of a digoxin therapeutic range of 0.8 to 2.0 ng/mL has been challenged, especially for the management of heart failure.[9–11] It is believed that a lower therapeutic range is equally effective in managing symptoms without subjecting patients to an increased risk of toxicity. Another important factor is renal function, because ~60% to 80% of digoxin is eliminated by the kidneys.[12] Because elderly patients may have renal dysfunction and/or a low lean body mass, they may be subject to a higher risk of digoxin toxicity because of a decrease in CL/F and a decrease in V_d of the drug.[9,13] Therefore, close therapeutic monitoring is necessary in this age group.

Studies have reported that there may be a high incidence of inappropriate use of digoxin in the elderly in terms of indications, dosing, or monitoring.[7,14–16] Miaiaszek et al[7] evaluated digoxin utilization in a retrospective chart review in 24 long-term care facilities in Canada, representing 1223 residents. Thirty-three percent of the doses were deemed to be in excess of those required to maintain a therapeutic effect. The therapeutic doses were calculated based on the patients' creatinine clearance adjusted for estimated lean body weight and body surface area, and a dosing nomogram for achieving therapeutic peak body stores of 6 to 10 μg/kg.[17] Therapeutic drug monitoring was performed in only 71% of the patients taking digoxin.[7] Budnitz et al[14] evaluated the risk of emergency department visits for medication adverse events in adults aged ≥65 years and found that 33.4% of the 177,504 visits were related to 3 medications, namely warfarin (17.3%), insulin (13.0%), and digoxin (3.1%).

In recent years, there has been a resurgence of interest in using digoxin, especially for the management of acute heart failure. Many of the data pertaining to digoxin are old because clinical studies were done in the era before the routine use of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists for heart failure management. Some investigators believe that the role of digoxin may need to be redefined, especially in the modern age of heart failure management.[18]

This article reviews the available clinical evidence on the therapeutic use of digoxin in elderly patients and the changes in the pharmacokinetics of digoxin with aging. Recommendations are made regarding dosing and monitoring to ensure optimal use of the drug in this patient population.

METHODS

Peer-reviewed clinical trials, review articles, and relevant treatment guidelines published in English and limited to those evaluating patients aged >65 years were identified from MEDLINE and the Current Contents database (both from 1966 to May 1, 2010) using the search terms *digoxin, pharmacokinetics, heart failure,* and *atrial fibrillation*. Citations from available articles were also reviewed for additional references.

RESULTS

One pharmacokinetic study, 8 clinical trials, and 2 guidelines were identified as relevant to digoxin use specifically in the elderly and are discussed in this article.[1,2,4,9–11,15,16,19–21]

Pharmacokinetic Profile of Digoxin

Physiologic changes related to aging, comorbid conditions, impaired homeostatic mechanisms, and polypharmacy alter the pharmacokinetic profiles of many medications, including digoxin, in the elderly population.[22] Aging affects drug absorption, distribution, bio-

transformation, and elimination, and these changes may consequently alter drug responses.[23] A better understanding of how aging affects the pharmacokinetic processes of digoxin may allow clinicians to predict drug responses and prevent drug-related toxicities.

Pharmacokinetics of Digoxin in the General Population

After oral administration, digoxin is absorbed by passive, nonsaturable diffusion through the intestinal wall.[24] The presence of food may reduce peak absorption, but does not alter the extent of absorption of the drug (peak serum digoxin concentration: with food, 1.5 ng/mL; fasting, 2.4 ng/mL; mean digoxin concentration: with food, 0.9 ng/mL; fasting, 1.1 mg/mL; *P* value not provided).[25] In up to 10% of patients, a digoxin-inactivating colonizing bacterium, *Eubacterium lentum*, has been associated with a reduction in digoxin bioavailability by converting digoxin into an inactive reduction product in the gastrointestinal (GI) tract.[26]

Digoxin is a highly polar glycoside with an apparent V_d ranging from 5.0 to 7.3 L/kg.[12] It does not have extensive protein binding (20%–25%). At steady state, digoxin binds to lean tissues, particularly myocardium, kidney, skeletal muscles, and red blood cells.[27] Body fat composition has no significant effect on digoxin pharmacokinetics because it is poorly lipophilic. Dialysis or other forms of ultrafiltration have no significant effect on plasma digoxin concentrations because the concentration ratio of myocardial to plasma digoxin is 50:1, and almost half of the total-body digoxin is bound to skeletal muscles.[28]

Renal elimination is responsible for ~60% to 80% of digoxin excretion in the general population.[29] Digoxin is excreted unchanged in the urine by passive glomerular filtration and active tubular secretion. The remaining drug (approximately one third) is eliminated by a nonrenal route: biliary excretion and hepatic biotransformation. Intestinal excretion of unaltered digoxin is responsible for 20% to 40% of total-body clearance, and only a small fraction (14%–16%) is metabolized by the liver.[30] Part of the clearance of digoxin via the renal and intestinal routes is believed to be due to active transport by P-glycoprotein.[31] The elimination $t_{1/2}$ of digoxin is 30 to 40 hours in patients with normal renal function. Given its long $t_{1/2}$, digoxin reaches steady-state concentration in ~8 days if no loading boluses are given.[32]

Pharmacokinetic Changes of Digoxin in the Elderly

Because digoxin has been used for centuries, research evaluating the effects of age on the pharmacokinetics of digoxin is dated and involves only a small number of patients. One study was identified that directly compared digoxin pharmacokinetics in 6 younger patients (aged <65 years; range, 32–61 years) and 7 elderly patients (aged ≥65 years; range, 71–91 years).[19] The results reported some significant changes in selected pharmacokinetic parameters of digoxin in the elderly, as discussed in more detail below (**Table I**).

Physiologic changes that occur with age may affect drug absorption. For example, elevated gastric pH in the elderly may result from atrophic changes in the gastric mucosa.[33] Declining GI motility or erratic emptying of the stomach contents into the duodenum has also been reported in the elderly.[34,35] Age-related decreases in GI or splanchnic blood flow may also reduce drug absorption.[33] In the study by Cusack et al,[19] digoxin pharmacokinetics were compared in younger patients given 0.5-mg single doses and elderly patients given 0.25-mg single doses, both administered intravenously and orally, 1 week apart. This study found no significant differences in the extent of digoxin absorption (**Table I**).

Drug distribution can be affected in a number of ways because of age-related changes in body composition. Total-body water and lean body mass may decrease by 10% to 20% with increasing age.[33] The study by Cusack et al[19] did not report a significant difference in the mean (SD) digoxin V_d after adjustment for the patients' total body weight (age <65 years, 5.3 [0.6] L/kg; age

Table I. Pharmacokinetic parameters of digoxin in younger versus elderly patients.* Data are expressed as mean (SD), except as indicated.

Parameter	Age <65 Years (n = 6)	Age ≥65 Years (n = 7)
Dose, mg	0.5	0.25
$t_{1/2}$ oral, h†	36.8 (4.5)	69.6 (13.1)
$t_{1/2}$ IV, h†	38.2 (3.5)	68.8 (12.3)
AUC oral, mmol/mL/h	89.7 (9.0)	144.6 (39.8)
AUC IV, mmol/mL/h	109.8 (15.5)	171.8 (32.8)
% Absorbed	84.3 (6.5)	76.0 (10.0)
V_d, L/kg	5.3 (0.6)	4.1 (0.9)
CL/wt, mL/min/kg†	1.7 (0.2)	0.8 (0.2)

CL/wt = total-body clearance adjusted for body weight.
* Reprinted with permission.[19]
† $P < 0.05$.

≥65 years, 4.1 [0.9] L/kg; **Table I**). However, a different conclusion was reached in another pharmacokinetic study evaluating V_d in 18 patients with different levels of renal function (6 with creatinine clearance <10 mL/min, 6 with creatinine clearance 10–50 mL/min, and 6 with creatinine clearance >50 mL/min).[36] This study reported that the V_d of digoxin was significantly reduced with severe decreases in renal function (4.8 vs 6.6 vs 6.4 L/kg in patients with creatinine clearance of <10, 10–50, and >50 mL/min, respectively; $P < 0.01$ for group 1 vs group 2 and group 1 vs group 3; P = NS for group 2 vs group 3). Because renal function is reduced with age, the V_d of digoxin in elderly patients may be lower than in younger patients.[33] Therefore, loading doses of digoxin may need to be reduced to accommodate the low V_d of digoxin in elderly patients who have decreased renal function. For instance, an elderly patient who weighs 70 kg and has creatinine clearance of <10 mL/min would need a loading dose of 0.336 mg IV (70 kg × 4.8 L/kg × 1 μg/L) to achieve a digoxin serum concentration of 1 ng/mL (or μg/L). If the same patient has creatinine clearance of >50 mL/min, the loading dose required to achieve the same therapeutic concentration would be 0.448 mg (70 kg × 6.4 L/kg × 1 μg/L).

Aging can also diminish the functional capacity of the renal elimination system. The glomerular filtration rate declines with age, and reductions are found in kidney size and the number of functional nephrons.[37] The study by Cusack et al[19] reported that the mean (SD) digoxin $t_{1/2}$ was significantly prolonged in elderly patients compared with younger patients (oral dosing, 69.6 [13.1] vs 36.8 [4.5] hours; IV dosing, 68.8 [12.3] vs 38.2 [3.5] hours; both, $P < 0.05$), and total-body clearance was significantly decreased (0.8 [0.2] vs 1.7 [0.2] mL/min/kg; $P < 0.05$) (**Table I**). These observations suggest that digoxin dosing intervals should be extended or the maintenance dose should be decreased in elderly patients to prevent accumulation of drug and the risk of adverse events.

Clinical Evidence on Digoxin Use in the Elderly

Heart Failure

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines[2] recommend that digoxin be added to the heart failure regimen in patients who have left ventricular systolic dysfunction with symptoms that persist despite optimization of treatment with an ACE inhibitor, a β-blocker, and/or a diuretic. The use of digoxin in heart failure was assessed in a long-term (2–5 years), randomized, double-blind, placebo-controlled study by the Digitalis Investigation Group,[1] which enrolled 6800 patients (mean age, 63.5 years) with heart failure symptoms and LVEF ≤45%. Digoxin was not associated with a significant effect on mortality compared with placebo (risk ratio = 0.99; 95% CI, 0.91–1.07) but was associated with a reduced risk of hospitalization for worsening heart failure (risk ratio = 0.72; 95% CI, 0.66–0.79; $P < 0.001$). It was reported that 26.7% of patients in the digoxin group and 27.4% in the placebo group were aged >70 years, and the beneficial effects of digoxin were not significantly different across all age groups (mortality or heart failure hospitalization: 21.5% for age <50 years, 29.3% for 50–59 years, 28.4% for 60–69 years, 32.4% for 70–79 years, and 29.4% for age ≥80 years).[9]

Elderly patients have a higher risk of digoxin toxicity (all toxicity included: 18.7% in patients receiving digoxin vs 10.8% in those receiving placebo) because of a higher incidence of renal dysfunction and/or low lean body mass, which prolong the digoxin $t_{1/2}$, as discussed previously.[9] The ACC/AHA guidelines[2] recommend a conservative dosing strategy for elderly patients with heart failure. For example, an initial dosage of 0.125 mg daily or every other day should be used in patients aged >70 years. A loading dose of digoxin is not necessary in heart failure management because the goal of treatment is a long-term reduction in the risk of hospitalization, not an acute effect in reduction of symptoms. Evidence suggests that digoxin should be dosed to achieve a serum drug concentration of 0.5 to 1.0 ng/mL in heart failure, even though the conventional therapeutic digoxin concentration is defined as 0.8 to 2.0 ng/mL. There are no prospective, randomized assessments of the relative efficacy or tolerability of various plasma concentrations of digoxin in the elderly. However, a retrospective analysis of data from 2 randomized, double-blind, placebo-controlled studies of digoxin withdrawal[38,39] in 139 patients with heart failure found no significant difference in the prevention of worsening heart failure whether digoxin was used at a lower concentration (0.5–0.9 ng/mL) or a higher concentration (>0.9 ng/mL).[10] In a post hoc analysis of the Digitalis Investigation Group trial (n = 6800 patients with LVEF ≤45%),[11] risk-adjusted mortality increased as the serum digoxin concentration exceeded 1 ng/mL (29.9% in those with concentration of 0.5–0.8 ng/mL, 38.8% in those with concentration of 0.9–1.0 ng/mL, and 48.0% in those with concentration >1.0 ng/mL; $P < 0.001$).

Atrial Fibrillation

The ACC/AHA guidelines for atrial fibrillation recommend the use of intravenous digoxin to control the

ventricular rate in patients with atrial fibrillation and heart failure.[4] The guidelines also recommend the use of oral digoxin to control the resting heart rate in patients with atrial fibrillation. This strategy is indicated for patients with heart failure, left ventricular dysfunction, or a sedentary lifestyle. When using digoxin to control the ventricular rate in atrial fibrillation, a loading dose is necessary to help achieve the therapeutic effect sooner. The ACC/AHA guidelines recommend a loading dose of 0.25 mg IV every 2 hours, up to a total of 1.5 mg based on heart rate and symptoms. Afterward, a maintenance dose of 0.125 to 0.375 mg/d can be given orally. No dosing specifically for the elderly was provided. This dosing strategy is more aggressive than the one used for heart failure management. Therefore, close monitoring of digoxin toxicity, especially during the loading dose, is essential. Digoxin is not recommended for controlling heart rate in atrial fibrillation during exercise, in paroxysmal atrial fibrillation, or in atrial fibrillation in a relatively younger patient population because the sympathetic nervous system activities in these relatively younger patients are generally higher, and digoxin is not efficacious in this circumstance.

Although intravenous digoxin may slow the ventricular response, its onset of action is delayed compared with other rate-control agents such as intravenous calcium channel blockers (eg, diltiazem) and β-blockers.[20] A randomized, open-label study compared the effects of intravenous diltiazem and digoxin on ventricular rate control in 30 patients (mean age, 72 years) with acute atrial fibrillation and flutter. Diltiazem was administered at 0.25 mg/kg IV over the first 2 minutes, followed by 0.35 mg/kg at 15 minutes and then a titratable infusion of 10 to 20 mg/h IV; digoxin was administered at 0.25 mg IV, given as a bolus at time 0 and at 30 minutes. In this study, diltiazem was associated with a significantly greater reduction in heart rate than digoxin at 5 minutes (mean [SD] heart rate, 111 [26] beats/min for diltiazem and 144 [13] beats/min for digoxin; $P = 0.001$). The decrease in heart rate with digoxin did not reach statistical significance for the comparison with baseline until 180 minutes ($P = 0.01$).

The ability of digoxin to control the ventricular rate is believed to be caused by its vagotonic effect on the atrioventricular node.[4] Therefore, its effectiveness in controlling ventricular heart rate is reduced in states of high sympathetic tone.[21] In an open-label, randomized crossover study evaluating the efficacy of various regimens for ventricular rate control, 12 patients with chronic atrial fibrillation (mean age, 69 years) were assigned to receive 5 regimens in random order, each for 2 weeks, as follows: (1) digoxin 0.25 mg/d PO; (2) diltiazem sustained-release 240 mg/d PO; (3) atenolol 50 mg/d PO; (4) digoxin 0.25 mg/d PO + diltiazem sustained-release 240 mg/d PO; and (5) digoxin 0.25 mg/d PO + atenolol 50 mg/d PO. The 24-hour mean heart rate values were reported as follows: for digoxin, 78.9 beats/min; for diltiazem, 80.0 beats/min; for atenolol, 75.9 beats/min; for digoxin + diltiazem, 67.3 beats/min; and for digoxin + atenolol, 65.0 beats/min ($P < 0.001$, digoxin + atenolol vs digoxin alone; $P < 0.001$, digoxin + atenolol vs diltiazem alone; $P < 0.001$, digoxin + atenolol vs atenolol alone). During exercise, the digoxin group had the highest mean ventricular rate (125 beats/min). This was significantly higher than the rates for diltiazem (105 beats/min; $P < 0.02$), atenolol (93 beats/min; $P < 0.005$), digoxin + diltiazem (102 beats/min; $P < 0.03$), and digoxin + atenolol (82 beats/min; $P < 0.001$).

Therefore, given the availability of other rate-control agents such as β-blockers and calcium channel blockers, which have a faster onset of action and are more efficacious in controlling heart rate both at rest and during exercise, digoxin is no longer considered a first-line therapy for the rapid management of atrial fibrillation.[4] Exceptions may include patients with heart failure or left ventricular dysfunction, patients whose blood pressure is low who may not be able to tolerate the hypotensive effect of β-blockers and calcium channel blockers, or perhaps patients who are so sedentary as to obviate the need for rate control during activity. Because, as indicated earlier, the prevalence of heart failure is high among the elderly (reaching 65.2 per 1000 population at age ≥85 years), many of whom have a sedentary lifestyle compared with a younger population, digoxin may be an appropriate choice for ventricular rate control in these subgroups of elderly patients.

Studies of Appropriate Use of Digoxin in the Elderly

Studies have evaluated the appropriateness of utilization of digoxin in elderly nursing home residents. In a study investigating the reasons for digoxin discontinuation among the elderly, the medical records of 342 nursing home residents aged ≥65 years were examined retrospectively.[15] Residents who had normal sinus rhythm and LVEF of ≥50% were considered candidates for discontinuation of digoxin. Forty-seven residents were taking digoxin therapy. Of 23 residents who met the criteria for withdrawal of digoxin, the attending physicians agreed to discontinue digoxin in only 14 of these residents. Their justification for refusing to discontinue treatment was that they believed the nursing home staff

was not able to provide sufficient monitoring of residents after discontinuation of digoxin. Of the 13 residents who discontinued digoxin, one patient had a decrease in LVEF from 60% to 50%, and digoxin therapy was resumed. No adverse events were reported in the other patients whose digoxin therapy was withdrawn. The duration of follow-up was 2 months. On the basis of these findings, the authors concluded that digoxin therapy may be discontinued safely if the original reason for prescribing it has resolved or if digoxin was initially prescribed for an inappropriate indication.

Another study reported the prevalence of appropriate and inappropriate use of digoxin in elderly nursing home residents (mean age, 81 years).[16] In this study, 96 of 500 consecutive admissions to the nursing home were identified as having a prescription for digoxin on admission. At the time of admission, those who were receiving digoxin were taking a daily dose ranging from 0.125 to 0.5 mg. Only 51 residents (53%) had an appropriate indication for digoxin therapy (ie, atrial fibrillation and/or heart failure with abnormal LVEF). Inappropriate indications for digoxin included heart failure with sinus rhythm and normal LVEF (18 patients [19%]), misdiagnosis of edema or dyspnea as heart failure (17 patients [18%]), possible history of (undocumented) paroxysmal atrial fibrillation (9 patients [9%]), and sinus tachycardia (1 patient [1%]).

These utilization evaluations indicate that there may be a high level of inappropriate digoxin use in elderly patients. Given that the elderly may be at higher risk of digoxin adverse events because of changes in the pharmacokinetic disposition of the drug,[9] these studies suggest the need to review the indications for digoxin to ensure appropriate use in this population.

Using Digoxin Appropriately in the Elderly

Besides ensuring that the indication and dosage are appropriate, physicians treating elderly patients with digoxin should also monitor this population closely for adverse events, including GI symptoms (nausea and vomiting; prevalence, ~10%), neurologic symptoms (visual disturbances; prevalence, ~15%), and cardiac arrhythmia (prevalence, ~3%).[39] These patients have a high intrinsic risk of sinus and/or atrioventricular block due to fibrosis of the sinus or atrioventricular node, and digoxin use can worsen such a block.[40,41] Therefore, unless the block has been addressed with a permanent pacemaker, digoxin should not be used.[2] Because elderly patients may be receiving many concurrent medications, they should also be monitored for drug–drug interactions. Clinically important drug–drug interactions can occur with digoxin plus amiodarone, quinidine, and verapamil (**Table II**). The dosage of digoxin should be reduced by 50% if treatment with one or more of these drugs is initiated.

DISCUSSION

Digoxin is a well-established agent for managing heart failure and for controlling a rapid ventricular rate in patients with atrial fibrillation.[42] Despite the high prevalence of digoxin use in the elderly, clinical studies evaluating the therapeutic effectiveness and dosing of digoxin in this population are scarce. Only one small study was identified that compared the pharmacokinetic profile of digoxin in younger versus elderly patients. That study indicated that the $t_{1/2}$ of digoxin may be prolonged and its clearance decreased in the elderly.[19] It is important to note, however, that the study was not done in patients with heart failure or atrial fibrillation, the group in which digoxin is to be used. It is not known whether digoxin

Table II. Important drug–drug interactions with digoxin.

Interacting Drug	Recommendations for Minimizing Risk of Digoxin Toxicity
Amiodarone	Initiating digoxin: 0.125 mg/d PO for normal renal function, 0.125 mg PO every other day for renal dysfunction (creatinine clearance <30 mL/min). Already taking digoxin: reduce dose by 50%.
Quinidine	Decrease digoxin dose by 50%.
Verapamil	Decrease digoxin dose by 50%.
Clarithromycin, cyclosporine, diltiazem, erythromycin, itraconazole, ketoconazole, propafenone	Monitor digoxin serum concentrations closely and adjust dose accordingly.

disposition is different in elderly people with heart failure or atrial fibrillation.

We found no studies that prospectively evaluated the therapeutic effectiveness of digoxin use specifically in elderly patients with either heart failure or atrial fibrillation. The retrospective subanalysis from the Digitalis Investigation Group study,[1] in which 1836 of the 6800 patients (27%) were aged >70 years, indicated that the benefits in terms of improving symptoms and reducing hospitalization from heart failure were not significantly different across age groups. A retrospective analysis of data from 2 studies of digoxin in patients with heart failure also reported no significant difference in clinical effect for a lower concentration of digoxin (0.5–0.9 ng/mL) versus a higher concentration (>0.9 ng/mL).[21] In the Digitalis Investigation Group trial,[11] risk-adjusted mortality increased as the serum digoxin concentration exceeded 1 ng/mL. This further suggests the importance of therapeutic monitoring of digoxin to ensure achievement of the very narrow therapeutic range and to minimize toxicity.

Similarly, few clinical trials have examined the therapeutic effectiveness of digoxin for ventricular rate control in the elderly patient population.[20,21] Nevertheless, it appears that given its vagotonic effect at the atrioventricular node, digoxin may be efficacious for ventricular rate control in elderly patients, who may have a sedentary lifestyle and low sympathetic nervous system activity.[43]

This article reviewed the limited published evidence evaluating the use of digoxin in the elderly population. This was not a systematic review, and therefore publication bias could not be ruled out.

CONCLUSIONS

The elderly population appears to gain comparable benefits as does a younger population from the use of digoxin for heart failure management in terms of symptom improvement and reduction of hospitalization. In atrial fibrillation, digoxin does not control the ventricular rate as efficaciously during exercise and in high adrenergic states as do β-blockers and calcium channel blockers. The elderly have reduced elimination of digoxin, so if digoxin is to be used, the dosing strategy must be conservative and therapeutic monitoring is needed. Further clinical studies are needed to confirm the pharmacokinetic parameters of digoxin in elderly patients with heart failure and/or atrial fibrillation.

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