Paper

Safe and effective use of digoxin in old age

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Abstract

Digoxin is a common cause of drug-related visits to emergency departments and of hospital admissions. This article promotes the safe prescribing of digoxin by reviewing appropriate indications for its use, manifestations of toxicity, appropriate dosing, therapeutic drug monitoring and clinical monitoring. The Digitalis Intervention Group trial and its post-hoc analyses have helped to redefine a lower and narrower therapeutic digoxin level of 0.6-1.2 nmol/L (0.5-0.9 ng/mL) in the treatment of heart failure. To ensure appropriate dosing clinicians must take into account inter-individual and intra-individual variability in pharmacokinetics and pharmacodyamics, which occur more commonly in older people.

Keywords

Digoxin, Appropriate use, Therapeutic range, Efficacy, Toxicity.

Search strategy

Pubmed/Medline/Ovid/ScienceDirect/Oxford Journals were searched using the terms: digoxin, serum concentrations, toxicity, intoxication, therapeutic drug monitoring, heart failure, atrial fibrillation, renal function, kinetics, elderly, safety; using the following limits: English abstracts, human studies, published up to October 2009.

Introduction

Withering introduced digitalis to the medical profession in 1785 by assuming that the foxglove plant *(Digitalis purpurea)* was the active ingredient of a herbal remedy for dropsy or oedematous states.[1] He warned that digitalis could be a potent poison if misused, and recorded its toxicity carefully in his 'Account of the Foxglove' lest the lives of men be "hazarded by its unguarded exhibition."[1] *"The foxglove when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death."*[1] Withering concluded that digitalis had a narrow safety margin and thus the importance of appropriate dose: just enough digitalis to cause diuresis, but not enough to cause vomiting or very slow pulse.[1] Inappropriate dosing and failure to recognize overdose remain as important in the causation of digoxin toxicity as Withering's description over 200 years ago, *"I recollect about two years ago being called to visit a traveling Yorkshire tradesman. I found him incessantly vomiting, his vision indistinct, his pulse forty in a minute. Upon enquiry it came out that his wife had stewed a large handful of green foxglove leaves in half a pint of water, and given him the liquor, which he drank at one draught, in order to cure him of an asthmatic affection. This good woman knew the medicine of her country, but not the dose of it, for her husband narrowly escaped with his life."*[1]

In 2006, Opie cautioned that "Today the US Food and Drug Administration (FDA) almost certainly would not license a drug (digoxin) that had such a narrow lethal to therapeutic margin of dose and blood levels."[2] Nevertheless, there is concern about the recent trend in the under-prescribing of digoxin given the published substantial morbidity benefits and overall safety of its use in heart failure.[3-7]

Older people are the most frequent users of digoxin because the two primary indications for its use, congestive heart failure and atrial fibrillation (AF), are highly prevalent in old age.[8-10] The narrow therapeutic window becomes more relevant in older individuals with multiple comorbidities and polypharmacy, where digoxin toxicity may remain unrecognized, leading to a further cascade of unnecessary prescriptions or investigations.[11] Adverse drug reactions (ADR) with digoxin are responsible for many older people attending emergency departments (EDs)[12] and being admitted to hospital.[13] This article aims to review how digoxin can be safely and effectively used in old age.

Efficacy and clinical uses of digoxin

Although the role of digoxin has been declining in recent years with the emergence of newer medications for heart failure[14] and AF,[15-16] it still has an important place in the management of such patients because of its documented economic and clinical benefits, reduced mortality in some subgroups, and easy availability worldwide.[3-4,6-7,17-18]

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Therapeutic efficacy in heart failure with sinus rhythm

The Digitalis Investigation Group (DIG) trial, the largest multicentre randomized clinical trial of digoxin use in heart failure with sinus rhythm (6800 patients, mean age 64 years, 27% aged > 70 years, ejection fraction ≤45%, mean 28%), demonstrated that treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalisation.[19] The use of digoxin was associated with a significant reduction (ARR 7.9%) in heart failure related hospital admissions among patients who were also receiving angiotensin-converting enzyme inhibitors (ACEI) and diuretics.[19] The authors estimated that about 50–65 hospitalisations would be prevented by the use of digoxin in 1000 person-years of treatment.[20] Differences in the rate of death from all causes (placebo group 35.1%, digoxin group 34.8%) were statistically insignificant.[19] However, the DIG trial was greeted with both negative[21] and positive[12,22] views on the clinical value of digoxin.

A subgroup analysis based on the DIG trial showed that discontinuation of long-term digoxin therapy was associated with increased hospitalisations with no effect on mortality and that continuation of long-term digoxin therapy at low serum digoxin concentrations of 0.6 - 1.2 nmol/L was associated with a significant reduction in mortality, all-cause hospitalisations, and heart-failure related hospitalisations.[23] A Cochrane review, which is dominated by the large DIG study, has shown a 64% improvement in symptoms (ARR 11.5%; NNT = 9) and a 23% reduction in hospitalisation (ARR 5.7%; NNT = 18) for patients receiving digoxin, but no survival benefit.[24]

In 2007, the Scottish Intercollegiate Guidelines Network (SIGN) guideline graded the recommendation on digoxin use in chronic heart failure as "A" based on the strong evidence from systematic review and randomized controlled trials, whilst cautioning that evidence of benefit must be weighed against digoxin toxicity.[25] In 2005, the American College of Cardiology changed the level of recommendation on the use of digoxin in chronic heart failure from Class I (should be administered) to Class IIa (reasonable to administer) because of its narrow risk/benefit ratio and absence of mortality benefit.[26-27]

Reviews[28-29] of current guidelines for the use of digoxin in heart failure[25-27,30-32] identify some discrepancies in their recommendations in terms of (see Table 1):

- levels of evidence
- classes of recommendations
- indication in sinus rhythm with left ventricular systolic dysfunction (ejection fraction <45%)
- and as an add-on therapy after optimum therapy (angiotensin converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], β-blocker, diuretics).

The American College of Cardiology further recommend that for a patient with heart failure who is taking digoxin but not an ACEI or a β- blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted; that digoxin is not indicated as primary therapy for patients with an acute exacerbation of heart failure symptoms, including fluid retention or hypotension; and that patients should not be given digoxin if they have significant and untreated sinus or atrioventricular block.[26-27]

	Scottish Intercollegiate Guidelines Network 2007	**European Society of Cardiology 2005**	**Canadian Cardiovascular Society 2006**	**Heart Failure Society of America 2006**	**American College of Cardiology/ American Heart Association 2009**
Sinus rhythm	Grade A: add-on therapy if still symptomatic after optimal therapy	Level A, class IIa: add-on therapy for LVSD if still symptomatic after optimal therapy	Level A, class I: add-on therapy for LVSD if still symptomatic after optimal therapy Level C, class IIb: for HFPEF	Level A*, class IIa: consider for LVSD with symptomatic heart failure	Level B, class IIa: add-on therapy for LVSD if still symptomatic after optimal therapy Level C, class IIb: for HFPEF
Atrial fibrillation	a beta blocker is preferred for rate control, though digoxin may be used initially while the beta blocker is being introduced	Level B, Class IIa: digoxin and beta-blocker appear superior to either agent alone	Level B, Class IIa: for poor rate control despite beta-blocker, or when beta-blockers cannot be used	Level B: for adequate rate control Level C: high digoxin dose (> 0.25mg daily for rate control not recommended	Adjunctive agent (on top of beta-blocker) for rate control

*Level A for NYHA class II-III, level B for NYHA class IV
LVSD = left ventricular systolic dysfunction
HFPEF = heart failure with preserved ejection fraction

Table 1. Comparison of recommendations for digoxin from international guidelines for treatment of chronic heart failure.

How applicable is the DIG Trial to heart failure in older people?

Increasing age had no influence on the effects of digoxin treatment on outcomes, although it was associated with increased hospitalisations for suspected digoxin toxicity and withdrawals from digoxin therapy.[33] However, patients recruited in the DIG trial, like the 59 heart failure randomized control trials conducted from 1985 to 1999, were younger (mean age was 64 years), less often female (22.4 % were female), and more likely to have reduced ejection fraction; a pattern that is markedly different from the majority of patients with heart failure in the community,[34-35] and especially those residing in long-term care facilities, who are primarily women, much older, with multiple comorbidities, on multiple medications, functionally impaired, and often with systolic function preserved.[36-38] Thus, the validity of generalizing the results of the DIG trial and its sub-analyses to older heart failure patients, especially the frailer ones, is questionable.[39]

In a retrospective cohort study of more than 19000 heart failure patients admitted to nursing homes in the US between 1992 and 1995 (mean age 85 years; 75% were female; mean number of non-cardiac diagnoses = 5; 4911 were taking an ACEI and 14890 were taking digoxin), digxoin-only users (as compared with those taking ACEI) were more likely to have functional decline (RR 1.35, 95% CI 1.25 to 1.45) and had a higher mortality rate (RR 1.12, 95% CI 1.05 to 1.20) after one year.[37] In a cross-sectional survey of 1223 residents in long-term care facilities in Canada, one-third of the residents with heart failure received digoxin. In 30% of patients, serum digoxin concentrations were greater than 1.5 nmol/L, a level higher than that currently recommended for optimal management of heart failure. At least 26% of these residents had comorbidities and concurrently prescribed medications that increase the risk of digoxin toxicity.[38] This emphasizes the necessity to exercise caution when using digoxin in long-term care residents, a frailer and much older group that are under-represented in randomized trials in heart failure.[38]

Digoxin has been considered contraindicated in patients with heart failure with preserved ejection fraction (HFPEF, also referred to as "diastolic heart failure"),[40-41] a common syndrome of heart failure in older age,[42] being thought to aggravate heart failure by increasing left ventricular stiffness and thus filling pressure through increasing contractility.[40] However, recent evidence has suggested that digoxin, at low concentration, can improve early myocardial relaxation through neurohormonal modulation in HFPEF.[4,43] In a parallel sub-study of the DIG trial that enrolled 988 patients (mean age 67 years, 64% aged >=65 years) with HFPEF in sinus rhythm (ejection fraction > 45%, mean 55%), the addition of digoxin to ACEI and diuretics resulted in an insignificant 18% reduction (p = 0.136) in the combined outcome of heart failure mortality or heart failure hospitalization.[44] The direction and magnitude of this finding are similar to that observed in patients with decreased systolic function. There was also a trend toward a reduction in heart failure hospitalizations (21% insignificant reduction; p = 0.094) that was balanced by a trend toward an increase in hospitalizations for unstable angina (37% insignificant increase; p = 0.061). The American College of Cardiology 2009 updated guideline[27] and the Canadian Cardiovascular Society guideline[31] state that the use of digitalis to minimize symptoms of heart failure in patients with HFPEF might be considered (recommendation class: IIb; level of evidence: C).

Use of digoxin in atrial fibrillation

Digoxin and other cardiac glycosides have been used for rate control in AF. Digoxin slows ventricular response to AF through enhancement of vagal tone, but has limited efficacy in states of increased sympathetic tone such as exercise, fever, thyrotoxicosis, acute volume loss, and postoperative state,[14,45-46] when β-blockers and non-dihydropyridine calcium-channel blockers (e.g. diltiazem) are more effective.[47]

Current clinical guidelines recommend that digoxin monotherapy may only be adequate for control of ventricular rate in the older, sedentary patient with permanent AF.[16,48-49] Combining digoxin with either a β-blocker or non-dihydropyridine calcium channel blocker may be done to achieve optimal heart rate during activity.[16,48,50-51]

Digoxin is not recommended for acute treatment of rapid ventricular response to AF in settings associated with high sympathetic tone (a helpful question to ask is, if the patient were in sinus rhythm would they have a sinus tachycardia) or a haemodynamically compromised state due to its slow onset of action, possible adrenergic activity and lack of efficacy in these conditions.[14,16,47-49,52] Digoxin, by blocking the AV node, will unmask or exacerbate a rapid AF due to a ventricular pre-excitation (i.e. Wolff-Parkinson-White syndrome) and is therefore contraindicated in such patients.[16,48] Digoxin should not be used as the sole agent for rate control in patients with paroxysmal AF, because of its lack of efficacy in states of high sympathetic tone, a possible precipitant of paroxysmal AF.[16,48,53]

Use of digoxin in heart failure with chronic atrial fibrillation

Though digoxin is prescribed routinely in patients with heart failure and chronic AF, β-blockers are usually more effective when added to digoxin in controlling the ventricular rate, especially during exercise.[54-55] Because β-blockers improve survival and may be effective in controlling rate alone, they are preferred for patients with heart failure and AF, though digoxin may be used initially while the β-blocker is being introduced.[25-27] Alternatively, digoxin may be used as adjunct therapy to β-blockers in patients with AF and heart failure because of its synergistic effect with β-blockers on the AV node in rate control. Enhanced survival with the digoxin-carvedilol combination has been demonstrated in a retrospective analysis of the US Carvedilol Heart Failure Trials program.[56] Though non-dihydropyridine calcium channel blockers (including verapamil and diltiazem) also

Study	Setting	Mean age (yrs)	Prevalence of digoxin use	Inappropriate indication for digoxin use
Ahmed[57]	Older heart failure patients at discharge from hospital (n=603)	79 ± 7 years	62%	59%
Aronow[58]	Older patients on admission to a nursing home (n=500)	81 ± 8 years	19%	47%
Fishkind[59]	Primary care outpatient geriatrics practice (n=528)	81 ± 8 years	17%	43%

Table 2. Studies on inappropriate use of digoxin in old age.

are effective rate-controlling agents, they may not be tolerated at doses required for optimal ventricular rate control because of their negative inotropic effect, especially in patients with low ejection fraction.

Inappropriate use of digoxin in older age

There is a high prevalence of digoxin usage at discharge from hospital for heart failure, on admission to a nursing home, or at follow-up in a primary care geriatric practice (62%, 19%, and 17% respectively).[57-59] In all three settings, digoxin use was inappropriate in around half of patients (Table 2),[57-59] e.g. misdiagnosis of edema or dyspnoea as congestive heart failure, paroxysmal atrial fibrillation, sinus tachycardia, coronary artery disease.[57-59]

Digoxin toxicity in older age

The many faces of digoxin toxicity in older age

Besides cardiac arrhythmias and heart block, older patients are also more likely to exhibit the nonspecific manifestations of digoxin toxicity such as anorexia, nausea, vomiting, malaise, weight loss, falls, weakness, visual disturbances, delirium, and neuropsychiatric symptoms.[60-62] Over a 3-month period, 33 of 2009 patients, with digoxin levels assayed, had definite toxicity; nausea was the commonest symptom (42%).[63] In a 1-year study of 109 in-patients, with therapeutic digoxin monitoring, a significantly higher proportion (58.5% vs. 8.6%, p = 0.0001) of the toxic patients (mean age 76.6 years) had gastrointestinal symptoms compared with the non-toxic group (mean age 71.7 years).[64] Neuropsychiatric symptoms and delirium may be the first and only manifestation of digoxin toxicity without accompanying electrocardiographic abnormalities in older patients, and can occur at serum concentrations within or above the therapeutic range.[65-67] When delirium complicates an already complex syndrome, the drug is often not suspected,[68] and it may form part of the picture of Wernicke's encephalopathy from thiamin deficiency secondary to prolonged anorexia from digitalis intoxication.[69] In a meta-analysis of 29 observational studies on medication use and falls risk, use of digoxin was found to be significantly associated with falls (OR = 1.2).[62] The clinical features of digoxin overdose in old age (fatigue, nausea, tachycardia) may not be identified as such, especially when the serum digoxin concentration falls within the "normal" range, and may be mistakenly attributed to the underlying condition of heart failure, leading to a prescribing cascade that completes the vicious cycle of overdosing the patient with digoxin (Figure 1).

Digoxin as an important cause of adverse drug reaction in older people

In both in-patients and out-patients increased age is

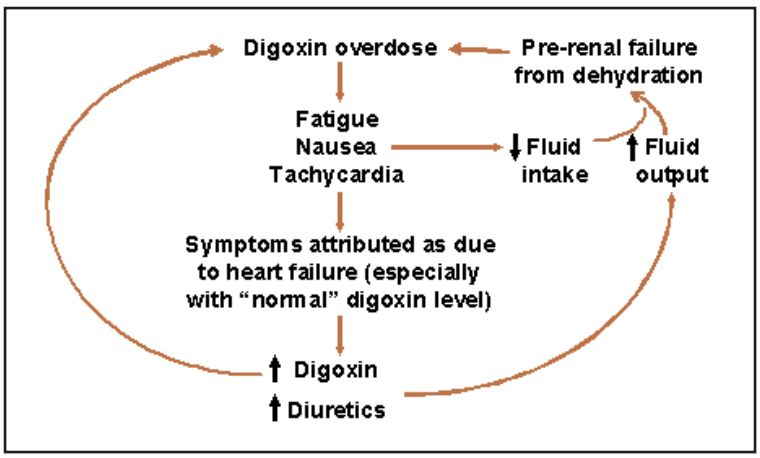

Figure 1. Failure to recognize digoxin overdose results in a prescribing cascade that completes the vicious cycle.

Ageing	Diseases/Conditions	Drugs
• Age-related reduction in volume of distribution of hydrophilic drugs • Age-related decline in glomerular filtration rate	• heart failure • early phase post-myocardial infarction • renal failure • low lean body mass • hypothyroidism • hypokalaemia • hypomagnaesaemia • acid-base imbalance • hypoxia • acute and chronic lung disease • dementia • dehydration • malnutrition	• Furosemide (hypokalaemia, dehydration) • Amiodarone • Verapamil • Oral macrolide antibacterials • Non-steroidal anti-inflammatory drugs

Table 3. Factors that increase the risk of digoxin toxicity in old age.

associated with enhanced susceptibility to digoxin toxicity. Clinical evidence of toxicity may be seen in 26.5% of those aged over 71 years old taking digoxin.[70] Age over 80 – 85 years is an independent risk factor for ADR to digoxin at the time of hospitalisation.[71-72] Hospitalisation for suspected digoxin toxicity is associated with increasing age (0.67% aged 50–59 years, 1.91% aged 60–69 years, 2.47% aged 70–79 years, and 4.42% aged >80 years).[33]

Despite a significant decline in digoxin use from 2001 to 2004 the number of reported cases of toxicity may be increasing, especially among older heart failure patients.[73] A prospective 4-year study on nursing home residents identified digoxin toxicity as the third most common cause of ADR-related hospitalisations, accounting for 8% of such hospitalisations.[74] In Italy, in the 1990's, digoxin was the second most common drug (4.62%) associated adverse reaction diagnosed at admission in older people.[14] In 2004, digoxin was the third most common drug after warfarin and insulin causing ADR in those aged 65 years and over, leading to emergency department visits in the USA (3.2% of such visits).[12] Older adults who have been hospitalised are at significantly increased risk of further hospitalisation due to digoxin toxicity for up to 2 months after discharge.[75]

Why are older people so prone to digoxin toxicity?

Older people, especially the more frail, are prone to digoxin toxicity because of the combined effects of age related changes in pharmacokinetics and pharmacodynamics, multiple pathology and polypharmacy resulting in reduced digoxin clearance and increased drug sensitivity (Table 3).

Digoxin has a large volume of distribution (4 to 7 L/kg), mainly in relation to lean body mass, which decreases by approximately 20% between the ages of 20 and 70 years in healthy individuals, and probably more in the setting of chronic illness and renal failure.[76-79] The volume of distribution for digoxin reduces with age and possibly results in higher serum concentrations.[76,80]

Glomerular filtration rate (GFR) declines by approximately one-third between the ages of 20 and 90 years reducing the rate of renal clearance of digoxin.[81] However, this aged-related decline in GFR is not reflected by serum creatinine measurement because of a corresponding age-related decline in muscle mass. Since serum creatinine is not a reliable indicator of renal function in old age, an estimate of the glomerular filtration rate (eGFR) is important to guide the appropriate dosage of renally excreted drugs with a narrow therapeutic window such as digoxin. Most dosing guidelines use the Cockcroft-Gault formula:[81-83]

Cockcroft-Gault eGFR (ml/min) in SI units = [(140—age (years)) × bodyweight (kg)×1.23]/(serum creatinine (umol/L)) × 0.85 (if the subject is female)

The modification of diet in renal disease (MDRD) equation does not use body weight to estimate the GFR. The MDRD derived eGFR has not been validated for extremes of age or dose adjustment. Unadjusted for body surface area, in the presence of the reduced height and weight observed in normal aging, the MDRD is likely to overestimate renal clearance in older adults.[83]

Digoxin dosing based on eGFR must be supplemented by clinical acumen as these formulae tend to underestimate at higher ranges of creatinine clearance and overestimate in the lower ranges,[83-85] and are unreliable in sick hospitalized patients.[83,86] Serum digoxin concentrations rapidly rise as creatinine clearance/eGFR falls.[87] A reasonable rule of thumb is: use lower doses in small, old, females and even lower doses when the person is sick!

Older people with chronic heart failure have reduced renal function by virtue of ageing, heart failure, coexisting diseases (e.g. hypertension, diabetes mellitus), drugs (e.g. nonsteroidal anti-inflammatory drugs), and intercurrent causes of dehydration (e.g. diuretics, reduced fluid intake, diarrhoea). The elimination half-life of digoxin may be prolonged from 30 - 40 hours in those with normal renal function to 4 - 6 days (or longer) in those with impaired renal function.

Older patients are more likely to be taking drugs that interact with digoxin. Clinically significant drug interactions include diuretic-induced hypokalaemia (increases sensitivity to digoxin and reduces its clearance) and dehydration (reduces renal clearance). Some antiarrhythmics (amiodarone, verapamil, quinidine) raise serum digoxin concentrations by increasing its intestinal absorption and decreasing renal clearance through inhibition of p-glycoprotein, a membrane transport pump which modulates the oral absorption of digoxin and its renal excretion.[80,88] Concomitant use of macrolide antibiotics (clarithromycin, erythromycin) also increase digoxin levels and potentiate digoxin toxicity by eliminating digoxin-inactivating bacteria in gut flora.[89-90] High dose spironolactone and steroids may interfere with several digoxin assays and cause falsely low readings of serum digoxin concentration so that digoxin intoxication could occur should dosage be increased because of falsely low results.[91-92] In addition, hypokalaemia, hypomagnesaemia, myocardial ischemia, hypoxia, acute and chronic lung disease, acidosis, hypercalcemia, and hypothyroidism may cause digitalis toxicity despite normal serum digoxin levels.[93-94]

Optimizing digoxin dosage and therapeutic range

Therapeutic drug monitoring for digoxin became available in the 1970's. The therapeutic window for serum digoxin concentration (SDC) of 1.3-2.6 nmol/L (1–2 ng/mL) originated from studies on cardiac arrhythmia due to digoxin intoxication,[95-98] rather than on clinical efficacy. The incidence of digoxin-induced arrhythmia was reported to be related to the SDC: 10% at 2.2 nmol/L (1.7 ng/ml) and 50% at 3.2 nmol/L (2.5 ng/mL).[99]

Evidence for a lower therapeutic serum digoxin concentration in heart failure

A study of digoxin prescription records in 1993/1994 revealed that there were significantly greater proportions of low-dose prescriptions (62·5–187·5 μg) in the UK compared with France and the USA; and that the digoxin doses used in the UK (median dose 125 μg, mean 170 [SD 70] μg) were significantly lower than dosages in the USA (median dose 250 μg, mean 210 [100] μg), and France (median dose 250 μg, mean 230 [80] μg).[100] Cardiologists from the UK and USA also had greater proportions of high-dose prescriptions (≧250 μg) than non-cardiologists.[100] When benchmarked with the PROVED[101] (median dose 375 μg) and RADIANCE[102] (mean dose 380 μg) digoxin withdrawal trials which targeted at the traditional therapeutic SDC of 1.3 – 2.6 nmol/L (1-2 ng/mL), the authors raised concern of underdosing in the UK and among non-cardiologists for fear of digoxin toxicity.[100]

However, on reviewing the dose-response to digoxin, moderate dose digoxin (250 μg daily) provided no additional hemodynamic or autonomic benefit for patients with mild to moderate systolic heart failure over low dose digoxin (125 μg daily). This suggested that lower dose digoxin should be considered in patients with mild to moderate heart failure because higher doses of digoxin may predispose to arrhythmogenesis.[103]

In patients with chronic heart failure a 34% increase in mortality was found in those with high SDC (> 1.4 nmol/L or 1.1 ng/mL) when compared to those with SDC ≦1.4 nmol/L or 1.1 ng/mL.[104] Lower SDC are associated with fewer episodes of worsening heart failure.[105-106] Higher digoxin doses and SDC levels above 1.3 nmol/L (1.0 ng/mL) do not lead to additional benefit for heart failure, and may even be harmful (Table 4).[104,107,110-111] In particular, post-hoc analyses of the DIG trail revealed that low SDC (0.6 – 1.2 nmol/L or 0.5–0.9 ng/mL) significantly reduced mortality and hospitalisations in ambulatory patients with chronic systolic heart failure[107-109] and diastolic heart failure,[108-109] and that these low SDCs were strongly related to low-dose use of the drug (≤125 μg/day).[108-109] The studies by Ahmed[108-109] also did not find any sex difference as reported in a previous study.[112]

The beneficial effects of digoxin in both systolic and diastolic heart failure are thought to be primarily due to its inhibitory effect on the neurohormonal system,[43] and that these effects are optimal at low doses and low SDC.[11,43,103,107] As the SDC increases, the inotropic action of digoxin becomes stronger and overrides the therapeutic benefits provided by neurohormonal modulation. The resultant inotropic-associated increases in myocardial oxygen consumption and arrhythmogenesis may account for the higher risk of digoxin toxicity and the higher morbidity and mortality observed at higher SDC.[43,107,113-114]

Evidence of clinical efficacy of digoxin at the lower SDC and higher risk of toxicity and mortality at higher SDC, resulted in a revised lower therapeutic range for SDC in heart failure (0.6 - 1.3 nmol/L [0.5 - 1.0 ng/mL]).[26-27,115-117] Although there is some overlap in 'therapeutic' and toxic levels in the original study by Smith: 87% and 13% of patients with digoxin toxicity have SDC > 2.6 nmol/L (2.0 ng/mL) and 1.3 nmol/L < SDC < 2.6 nmol/L (1 ng/mL < SDC <2.0 ng/mL) respectively,[96] none have digoxin toxicity with the newly adopted therapeutic SDC of less than 1.3 nmol/L (1 ng/mL).[96]

Quoting the lower therapeutic digoxin range on computerized and printed laboratory report forms is therefore important to guide clinicians to avoid unnecessarily high SDC without compromising the benefit for heart failure.[118]

Lack of an optimal "therapeutic" serum digoxin concentration for the use of digoxin in atrial fibrillation

Relatively few studies have systematically evaluated the efficacy and safety profile of digoxin in AF.[119-120] Further systematic study is required.

In 30 patients with acute AF and 30 patients with chronic AF, digoxin was found to be relatively ineffective in controlling the ventricular rate at the traditional

Original Study				Sub-analysis (Low SDC vs High SDC studies)			
Ref.	**N**	**LVEF**	**Mean SDC**	**Ref.**	**Low SDC**	**High SDC**	**Outcome**
RADIANCE[102]	178 (85 on digoxin)	≦35%	1.5 nmol/L	105, 106	0.6 – 1.2 nmol/L	>1.2 – 1.5 nmol/L; >1.5 nmol/L	Low SDC group had fewer episodes of worsening heart failure during follow-up[105, 106]
PROVE[101]	88 (42 on digoxin)	≦35%	1.5 nmol/L				
DIG (main study)[19]	6800 (3397 on digoxin)	≦45%	1.1 nmol/L	107 (for men)	0.6 – 1.0 nmol/L	1.2 – 1.4 nmol/L; ≧1.5 nmol/L	0.6-1.0: lower mortality 1.2-1.4: same mortality as placebo ≧1.5: higher mortality
DIG (ancillary study)[44]	998 (492 on digoxin)	>45%	1.1 nmol/L	108, 109	0.6 – 1.2 nmol/L	≧1.3 nmol/L	Irrespective of LVEF; Low SDC reduced mortality & hospitalizations [108,109] High SDC reduced heart failure hospitalizations, but no effect on mortality or all-cause hospitalizations[108]

Table 4. Low SDC vs high SDC studies on use of digoxin in heart failure in sinus rhythm.

"therapeutic" SDC concentrations; and in some instances adequate rate control was only achieved at "toxic" SDC.[121] The poor correlation between SDC and resting heart rate in patients with AF may result in digoxin overdose if ventricular response is used as a yardstick for adjusting digoxin dose requirements.[97,122] Digoxin is also not effective in controlling heart rate during exercise at the traditional therapeutic SDC.[123-124] The American College of Cardiology guidelines caution that "Although digoxin continues to play a role in some patients with heart failure and AF, the traditional practice of arbitrarily increasing the dose and SDC of digoxin until ventricular response is controlled should be abandoned, because the risk of digoxin toxicity increases as well."[26-27]

A post hoc analysis of the AFFIRM study showed that digoxin was the sole rate-control drug for AF that was significantly associated with an increased risk of death (hazard ratio = 1.42, 99% CI 1.09 to 1.86).[125] Pooled data on 7329 patients with moderate-to-high risk AF from the SPORTIF III and V trials showed that digoxin users had a hazard ratio of 1.58 (95% CI 1.22 to 1.92) for mortality.[126] These studies were not randomized and so can not assess and correct for the complex social and behavioural determinants of digoxin use.[127] Nonetheless, it would appear that the AF and heart failure patient populations react differently to digoxin therapy, such that patients with heart failure may gain more benefit from digoxin use.[126]

Appropriate digoxin dosing and therapeutic serum digoxin concentration in older people

There are wide inter- and intra-individual variations in SDC amongst older people (aged >65 years) taking similar digoxin doses.[128-129] The overlap between toxic and non-toxic ranges of SDC is considerably greater than in younger patients[129] and tends to shift towards lower SDC.[70] The significant overlap between toxic and nontoxic levels of SDC in older age is probably related to the high prevalence of multiple factors that influence individual responses to digoxin (Table 3). Thus SDC must be interpreted in the overall clinical context in a frail older person with multiple comorbidities.[130-132]

A small efficacy study in older people (aged over 74 years, mean age 83.8 years) with congestive heart failure in sinus rhythm revealed an optimum serum digoxin concentration of 0.5 - 1.3 nmol/L (0.4 ng/mL – 1.0 ng/mL) at which ejection fraction was improved, and no further improvement in the mean ejection fraction with higher doses of digoxin to increase the serum digxoin concentration to above 1.3 nmol/L (1.0 ng/mL).[133]

With the demonstration of reduced mortality and hospitalisations in heart failure patients at SDC of 0.6 - 1.2 nmol/L (0.5 – 0.9 ng/mL),[107-109] the therapeutic range for heart failure has been referenced as 0.6 - 1.0 nmol/L (0.5 – 0.8 ng/mL) or 0.6 - 1.2 nmol/L (0.5 – 0.9 ng/mL) in geriatric texts published after 2006.[41,134-135]

Current recommendations are that a maintenance dose of digoxin should be 125 μg daily in most older men and women who have an estimated eGFR above 50 ml/min, and that lower doses (62.5 μg daily) should be used in those with lower eGFR and in heart failure patients with multiple risk factors for high SDC.[108-109,134-135,136] The need for precise digoxin dosing regimens tailored to the therapeutic range mitigates against the practice of prescribing digoxin for example 5 days a week, it is much better to give a small daily dose (e.g. 62.5 μg daily) especially when there is cognitive impairment.[137-138]

The SDC should be measured 2 - 4 weeks after starting digoxin:

- in patients with deranged renal function
- when used with agents that alter the disposition of digoxin
- or whenever digoxin toxicity is suspected,

to ensure that it is within the therapeutic range of 0.6 - 1.2 nmol/L (0.5 – 0.9 ng/mL).[108-109,134-135,139] Digoxin dosage should be adjusted and the SDC monitored in patients with an acute illness which might cause a decline in renal function and also when medication changes.[108-109,134-135,139]

The practice of using loading doses of digoxin to initiate therapy in patients with heart failure is especially risky in older age, given the reduced renal clearance of digoxin,[140] and is not recommended.[27] Therapeutic plateau tissue concentrations of digoxin can be achieved without a loading dose by the sixth day of a daily maintenance dose.[141] Loading doses of digoxin greater than 700 μg /day are almost invariably associated with side effects.[142] Loading doses are also potentially hazardous in patients with AF; 26 of 35 patients who developed high digoxin levels while in hospital had been loaded with digoxin,[122] despite the elevated digoxin level, rate control was achieved in only 11 of these 26 patients.

Conclusions

Clinicians must observe the indications for the appropriate use of digoxin and individualise digoxin dose according to renal function, which should be assessed using eGFR in older people and not serum creatinine alone. However, they should also be aware of the limitations and unreliability of eGFR formulae when applied to frail or acutely ill older people.[83] Associated comorbidities, acute illnesses and medications that impact on hydration and renal function, and potential drug interactions should also be taken into consideration in adjusting digoxin dosage. The transition of care from the inpatient to the outpatient setting is an especially vulnerable period.[75] When digoxin is prescribed, close monitoring is essential to ensure the correct dosage is prescribed and is being taken. The reasons given for non-adherence may indicate intolerance due to toxicity; a heightened vigilance must be maintained not only for the cardiovascular (arrhythmia), but also for the gastrointestinal (commonly nausea, vomiting, anorexia), and neuropsychiatric symptoms and signs of digoxin overdose. Any decline in functional level, such as recent confusion, instability and falls,[62] may also indicate digoxin toxicity.

Because the manifestations of digoxin toxicity in an older person can be non-specific, determination of SDC would be helpful when toxicity is suspected.[64] The limitation of therapeutic drug monitoring (TDM) must be remembered.[143] While digoxin TDM allows a clinician to compensate for factors that alter its pharmacokinetics (lean body mass, renal function, drug interactions), TDM cannot account for age-related changes in pharmacodynamic response to digoxin.[143-144] Thus, a SDC within the therapeutic range may not assure absence of digoxin toxicity, and clinical monitoring is just as important as TDM.[143] A useful rule of thumb in identifying any ADR is simply to ask oneself "could this patient's condition be due to one or more of the drugs they have taken?"[145] Disappearance of presumed toxic symptoms upon stopping digoxin may support the clinical suspicion of digoxin toxicity.[64]

Ensuring that laboratory reports include the latest, lower and narrower therapeutic range of SDC in heart failure, will help reduce the chance of the clinician overdosing the patient.[118] The use of automated clinical decision support computer technology, which screens the patient's electronic medical record for scenarios associated with an increased risk of digoxin toxicity and alerts the clinician for corrective action, may also reduce the chance of dosing errors.[146-148] "However, the role of the intracranial computer will remain paramount,"[149] and that means knowing the older person through comprehensive geriatric assessment, thinking carefully before prescribing and applying the principles of geriatric pharmacology in the appropriate care of the older person on digoxin.[83,150-153]

Safe and effective use of digoxin in old age

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