Digoxin in the 21st century

Christopher Semsarian, Associate Cardiologist, Royal Prince Alfred Hospital, Sydney

SYNOPSIS

Digoxin is a relatively safe, cheap and effective therapy for relieving recurrent symptoms in patients with congestive heart failure. It should be used as an adjunct to treatments known to reduce mortality e.g. angiotensin converting enzyme inhibitors. The risk of digoxin toxicity can be minimised by using dosage regimens based on body weight and creatinine clearance, monitoring potential electrolyte imbalances and being aware of possible drug interactions. Particular caution is needed in the elderly who often require lower maintenance doses.

Index words: atrial fibrillation, heart failure, adverse effects, dose regimens.

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Introduction

The pharmacological management of congestive heart failure has improved significantly over the last decade. Several trials have shown that angiotensin converting enzyme (ACE) inhibitors improve long-term survival in patients with heart failure. More recently, angiotensin (AT_1) receptor blockers, beta blockers and carvedilol have also improved treatment strategies. These drugs, in combination with diuretics and vasodilators, remain the key drugs in the management of heart failure.

For over 200 years, debate over the use of digoxin in heart failure has continued unabated. Following the recent advances in the pharmacological treatment of heart failure, the role of digoxin has again been questioned. Does digoxin have a role in the management of heart failure in the 21st century amongst the abundance of new therapies?

Mechanism of action

Digoxin is a cardiac glycoside extracted from foxglove leaves. It is used in heart failure because of its ability to increase the force of myocardial contraction (positive inotropy) and, simultaneously, decrease oxygen consumption.

Digoxin binds to and inhibits the sodium/potassium-ATPase (sodium pump) within the plasma membrane of cardiac myocytes. This inhibition increases the intracellular sodium content which in turn increases the intracellular calcium content which leads to increased cardiac contractility.

Digoxin has other effects on the heart, particularly on its electrical activity. It also affects the contractile function of vascular smooth muscle and the activity of the autonomic nervous system.

Role of digoxin in heart failure

Historically, digoxin has been widely used to slow the ventricular rate (predominantly at rest) in patients with atrial fibrillation. However, digoxin has now been shown to improve symptoms in patients with moderate to severe congestive heart failure who are in sinus rhythm and are already taking ACE inhibitors and diuretics. The largest ever randomised, placebo-controlled, double blind trial of digoxin included 6800 patients with heart failure. The patients who started digoxin had a significant improvement in symptoms. This was associated with a near 10% reduction in hospital admissions during the follow-up period.[1] There was no difference in mortality in the digoxin-treated and control groups, although serum digoxin concentrations in the study group were at the lower end of the therapeutic range (approximately 0.8 ng/mL). This study has not excluded an adverse effect of digoxin at higher doses which produce plasma concentrations within the therapeutic range. The study shows that digoxin has a role in the treatment of heart failure in reducing symptoms, i.e. improving morbidity, in patients who are already receiving drugs which can reduce mortality e.g. ACE inhibitors. For example, a patient with heart failure who has recurrent symptoms, despite receiving an ACE inhibitor, a diuretic and a nitrate, may benefit from the addition of digoxin.

Anecdotal evidence has always suggested that withdrawing digoxin can make a patient's symptoms worse. This has been confirmed in recent trials which show a deterioration in both functional capacity/quality of life and in left ventricular systolic function.[2] In clinical practice, we must consider this 'withdrawal effect' when deciding whether to cease digoxin therapy in patients with heart failure.

Dose and administration

Digoxin is usually taken orally, with peak plasma levels occurring at 2-3 hours after an oral dose. Achieving steady state concentrations may take up to a week depending on whether a 'loading' dose is given, and also on the severity of heart failure, as the distribution of digoxin within the different compartments of the body is slower.

The serum digoxin concentration (optimally measured at least six hours after the last dose) is dependent on both dose and renal function. Digoxin is primarily eliminated by the kidney through filtration at the glomeruli and secretion by the tubules. The dose of digoxin in an individual can be calculated based on renal function (creatinine clearance) and body weight (Table 1).[3] Most patients require a dose of 0.125-0.25 mg/day to reach the therapeutic range of 0.5-2.0 ng/mL.

Table 1

Digoxin dosage regimen *(adapted with permission from reference 3)*

*Creatinine clearance (mL/min/70 kg)**	*Body weight (kg)*					
	50	*60*	*70*	*80*	*90*	*100*
	Daily digoxin dose (mg)					
10	0.125	0.125	0.125	0.125	0.250	0.250
20	0.125	0.125	0.125	0.250	0.250	0.250
30	0.125	0.125	0.250	0.250	0.250	0.250
40	0.125	0.250	0.250	0.250	0.250	0.250
50	0.125	0.250	0.250	0.250	0.250	0.250
60	0.250	0.250	0.250	0.250	0.250	0.375
70	0.250	0.250	0.250	0.250	0.250	0.375
80	0.250	0.250	0.250	0.250	0.375	0.375
90	0.250	0.250	0.250	0.250	0.375	0.500
100	0.250	0.250	0.250	0.375	0.375	0.500

* The corrected creatinine clearance was calculated as 140 - (age ÷ serum creatinine concentration in milligrams per decilitre) for men, and 140 - (age ÷ serum creatinine concentration) x 0.85 for women.

Note: In Australia creatinine concentrations are usually given in SI units. For an adult male the reference range is 0.06 - 0.115 mmol/L which is equivalent to 0.7 - 1.3 mg/dL. Multiplying the concentration in mmol/L by 11 gives an approximation of the concentration in mg/dL.

Table 2

Adverse effects of digoxin

Cardiac	atrioventricular conduction abnormalities ventricular arrhythmias
Gastrointestinal	anorexia, nausea and vomiting diarrhoea and abdominal discomfort
Neurological	headache, fatigue and drowsiness generalised muscle weakness confusion, hallucinations, 'digitalis delirium' blurred vision
Others	gynaecomastia, rash

Table 3

Common drug interactions

Interacting drugs	*Mechanisms*
Thiazide diuretics, acetazolamide, amphotericin B, frusemide	drug-induced hypokalaemia
Quinidine, diltiazem, verapamil, spironolactone, erythromycin, amiodarone	digoxin concentrations elevated
Adrenaline and related beta agonists	increased risk of arrhythmias

Adverse effects and digoxin toxicity

The adverse effects of digoxin are summarised in Table 2. Digoxin toxicity was first described by Withering in 1785, who described the signs of toxicity as follows:

'The foxglove, when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confined vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it; slow pulse, even as low as 35 in a minute, cold sweats, convulsions, syncope and even death.'

Digoxin toxicity can occur due to interactions with other drugs, unrecognised renal disease, alterations in plasma electrolytes and metabolic disturbances. Some commonly prescribed drugs can increase the toxicity of digoxin (Table 3). A common interaction is with diuretics which cause potassium depletion. Importantly, advanced age, with the associated changes in renal perfusion, creatinine clearance and volume of drug distribution, almost always requires the maintenance dose of digoxin to be reduced.

Management of digoxin toxicity may involve stopping the drug, correcting any imbalance in potassium and/or magnesium and treatment of specific arrhythmias. In certain cases, e.g. with severe haemodynamic compromise, Fab fragments of digoxin-specific antibodies may be required.

Conclusion

For most patients with congestive heart failure in sinus rhythm, digoxin remains an effective, safe and inexpensive drug for the relief of symptoms. Digoxin does not reduce mortality, so its role is in the treatment of persistent symptoms in patients who are already being treated with drugs that decrease the risk of death.

(See also *Dental Implications*: page 144)

REFERENCES

1. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-33.
2. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. N Engl J Med 1993;329:1-7.
3. Cohn JN. The management of chronic heart failure. N Engl J Med 1996;335:490-8.

Self-test questions

The following statements are either true or false (answers on page 151)

1. Diuretics may provoke digoxin toxicity.
2. Digoxin is the first-line treatment for patients with heart failure who are in sinus rhythm.