Mini-review

Digoxin revisited

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Introduction

Digoxin is a drug which has been around for a very long time. Since 1785, when William Withering described the use of digitalis in patients with dropsy, now recognized as heart failure, digoxin has been the subject of debate and controversy. Due to its convenient pharmacokinetics, alternative routes of administration, the widespread availability of techniques for its measurement in serum, and the fact that it is inexpensive, digoxin has become the most commonly prescribed cardiac glycoside in the 1990s. Indeed, digoxin is very commonly used for the control of the ventricular rate response in atrial fibrillation, and recent evidence has suggested some advantages in the management of heart failure. We discuss the clinical uses of digoxin, its mechanisms, factors that affect the accurate measurement of its concentration and dosage, and its usage in the treatment of heart failure.

Mechanisms of action

William Withering first used the purple foxglove, *digitalis purpurea*, which is now recognized to contain the cardiac glycoside, digitoxin. Most commercial digoxin is now derived from the leaves of *digitalis lanata*. Many of the mechanisms of action of the cardiac glycosides are now fairly well recognized.

Sodium-pump inhibition and inotropic effects

Digoxin is a potent and highly selective inhibitor of Na⁺K⁺-ATPase. This binding to, and inhibition of, the sodium pump is reversible, and permits sodium to remain in the cardiac cell, which is then expelled using a sodium-calcium exchange process. The latter results in a higher level of intracellular and myocardial calcium; the increased intracellular calcium leads to increased inotropism, accentuating the force of myocardial contraction by increasing the velocity and extent of sarcomere shortening, thus translating into increased stroke work for a given filling volume of pressure.

Regulation of sympathetic nervous system activity

Several studies have evaluated the neurohumoral and autonomic effects of digoxin. For example, the evidence suggests that digoxin tends to exert its inotropic effects at higher doses, whilst at lower
doses, less inotropism and more pronounced neuro-humoral effects are observed.11,12 Neurohormonal effects include the inhibition of renin release from the kidney, as digoxin decreases the activity of the renal sodium pump, leading to a natriuretic effect and vasodilation. This reduction in neurohormonal activation could represent an important additional mechanism contributing to the efficacy of digoxin in the treatment of heart failure.

Digitalis also appears to modulate sympathetic tone in a manner similar to that of its haemodynamic effects, and this can differ between healthy volunteers and patients with heart failure. In heart failure, for example, digoxin will generally have sympathoinhibitory effects, depending on the severity of the disease and on the dose used. Several potential explanations for the neuroinhibitory effects of digitalis in heart failure exist, but the observed improvement or normalisation of impaired baroreceptor-mediated mechanisms seems to play an important role. However, not all studies have supported this concept. Heart-rate variability has also been measured as an index of autonomic function, where the effects of digoxin on heart-rate variability indices have been studied, both in patients with heart failure and in normal subjects.

Electrophysiological actions

Digoxin is frequently used to control the ventricular rate in atrial fibrillation, alone or in conjunction with a β-adrenergic blocking agent, amiodarone or the calcium-channel antagonists, verapamil or diltiazem. This effect is a reflection of the electrophysiological actions of digoxin on cardiac tissue. However, atrial and ventricular myocardial cells, as well as the specialized cardiac pacemaker and conduction fibres, exhibit different responses and sensitivity to digoxin, which are generally a summation of the direct effects of the drug as well as indirect, neurally-mediated effects. At therapeutic, non-toxic serum or plasma concentrations (1.0–2.0 ng/ml), digoxin decreases automaticity and increases maximal diastolic resting membrane potentials, predominantly in atrial and atrioventricular nodal tissues; these effects are due to an increase in vagal tone and a decrease in sympathetic nervous system activity. There is also a prolongation of the effective refractory period and a decrease in conduction velocity in atrioventricular tissue. At higher concentrations of digoxin, these effects may cause sinus bradycardia or sinus arrest and/or prolongation of atrioventricular conduction and heart block.

Clinical indications

Digoxin is commonly used for ventricular rate control in chronic atrial fibrillation. However, digoxin is useful in controlling the resting heart rate, but less so in exercise or in conditions of high sympathetic tone, where a beta-blocker or calcium antagonist, such as verapamil or diltiazem, will be more effective. It still remains uncertain whether a strategy of heart-rate control (and anticoagulation) is superior with respect to long-term morbidity and mortality, when compared to a strategy of cardioversion and maintenance of sinus rhythm—many large trials are in progress to address this question. However, digoxin is certainly an ineffective drug for the cardioversion of atrial fibrillation to sinus rhythm, or the maintenance of sinus rhythm post-cardioversion.

The most solid indication for digoxin is still the combination of chronic heart failure with atrial fibrillation, where the combination of ventricular rate control and inotropism seems to benefit many patients. By contrast, the efficacy of digoxin in those who with heart failure and sinus rhythm has often been questioned. The evidence supporting the efficacy of digoxin in patients with heart failure who are in sinus rhythm is increasing, with many trials, such as the PROVED, RADIANCE and DIG trials (as discussed later). Although digoxin does not appear to reduce mortality in such patients, it does appear to improve haemodynamics, exercise capacity, symptoms and quality of life, with a significant reduction in hospitalizations. There is no evidence that digoxin controls the ventricular rate or terminates a paroxysm of paroxysmal atrial fibrillation. By contrast, there is some evidence that digoxin may in fact make paroxysmal atrial fibrillation worse, by increasing paroxysms of atrial fibrillation, and when these paroxysms do occur, they do so at even higher heart rates. In children, digoxin is preferred to diuretic therapy as first-line treatment of heart failure, even in high-output states with left or right shunts, although its efficacy is not without dispute.

Pharmacokinetics and dosing for digoxin

The elimination half-life for digoxin, which is 36 to 48 h in patients with normal or near-normal renal function, allows once-a-day dosing. In the absence of oral or intravenous loading doses, near steady-state blood levels are achieved within four half-lives, or about one week after initiation of maintenance therapy. In patients with heart failure and reduced cardiac reserve, increased cardiac output and renal blood flow in response to treatment with vasodilator or sympathomimetic agents may increase renal digoxin clearance, necessitating dosage adjustment.

Digoxin is not removed effectively by peritoneal or haemodialysis because of its large (4 to 7 l/kg)
volume of distribution. The principal body reservoir is skeletal muscle and not adipose tissue; accordingly, dosing should be based on the estimated lean body mass, which is often a source of confusion and inappropriate dosing. Neonates and infants may often tolerate and require higher doses of digoxin for an equivalent therapeutic effect when compared to older children or adults. It should be noted that digoxin does cross the placenta, and drug levels in maternal and umbilical vein blood are similar.

Establishment of the optimal dose of digoxin for its various indications is an important issue. Whilst it has been suggested that increasing digoxin dose to 0.39 ± 0.1 mg/day may improve left ventricular (systolic) function and increase inotropism, at lower doses the neurohormonal and vagotonic or sympa-tholytic effects predominate. While in clinical practice a therapeutic range of 1.0–2.0 ng/ml is used, data from the Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin (PROVED), the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme (RADIANCE) trials and other studies suggest that increasing the digoxin dose to cause serum levels above 1.2 ng/ml may be questionable, and levels of 1.5–2.0 ng/ml are probably unnecessary. However, it is difficult to compare serum digoxin concentrations among studies because there is no standardized time after dosing for obtaining serum levels, and several other technical problems may cause additional biases. It is well-recognized however that digoxin has a narrow therapeutic range, with only a small serum concentration ‘safe’ range.

Most generic digoxin tablet preparations average 70% to 80% oral bioavailability, with oral bioavailability of 90% to 100% for digoxin elixir and the encapsulated gel preparation. Parenteral digoxin is available for intravenous administration, and is of value in patients who are unable to take oral formulations. Although intravenous digoxin does begin to work sooner (<30 min) than oral digoxin (approximately 30–60 min, or more), it does not work instantaneously. In fact, oral digitalis with a loading dose of 1 mg produces peak blood levels of >1 ng/ml within 1–5 h and a maximum effect only after 4–6 h; by contrast, an intravenous loading dose of 0.75–1mg digoxin gives labile initial plasma digoxin levels (as high as 95 ng/ml, which may be potentially more dangerous). Thus, loading still takes several hours to have its maximum effect in slowing the rate, and caution is necessary in elderly patients or those with renal impairment. During oral administration, the bioavailability of the cardiac glycosides can be affected by concomitant disease states, such as heart failure, and some gut flora; for example, approximately 10% of the general population harbours the enteric bacterium Eubacterium lentum, which can convert digoxin into inactive metabolites. This may account for some cases of apparent resistance to standard doses of oral digoxin.

Therapeutic drug monitoring

Nomograms are available for estimating loading and maintenance doses of digoxin; however, these are not widely used because of the variability in individual patient responsiveness to cardiac glycosides and the ready availability in most clinical settings of serum in concentration assays. Blood samples for serum digoxin level measurement should be taken at least 6–8 h following the last digoxin dose. Adequacy of digoxin dosing and risk of toxicity in a given patient should never be based on a single isolated serum digoxin concentration measurement.

A number of clinical conditions and drug interactions can alter the pharmacokinetics of digoxin, which would be reflected in changes in serum levels of digoxin. For example, hypothyroidism and chronic renal failure significantly reduce the volume of distribution of digoxin, necessitating a decrease in both loading and maintenance doses of the drug. Hypochlorhydria and patients taking the histamine H2 receptor antagonist, cimetidine, reduce metabolism of digoxin and renal clearance of the drug, thus potentiating toxicity.

Many disease states and changes in serum electrolytes can change patient susceptibility to toxicity at any given dose or serum level of the drug. For example, hypokalaemia and hypomagnesaemia can independently increase ventricular automaticity and lower the threshold for digoxin-induced cardiac arrhythmias. Furthermore, retrospective analyses suggest that the use of digitalis in the setting of cardiac ischaemia, such as after myocardial infarction, may be associated with increased mortality, particularly in patients with ventricular arrhythmias. One postulated mechanism may be the finding of Indolfi et al. that digoxin may cause vasoconstriction of coronary arteries.

Many studies have suggested that there is a non-linear relationship between the serum level of digoxin and the observed inotropic effect, with most of the increase in contractility apparent at serum levels around 1.8 nM. The relationship between serum digoxin levels is, however, less clear in relation to the control of the ventricular rate in atrial fibrillation.

Drug interactions with digoxin

Many drugs exhibit potentially important pharmacokinetic drug interactions with digoxin. Many of these drugs, such as verapamil, quinidine and amiodarone,
Table 1 Drug interactions with digoxin

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Decreased renal excretion</td>
<td>Concurrent cardiac drugs (quinidine, verapamil, amiodarone)</td>
</tr>
<tr>
<td>Increased renal clearance</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>Decreased non-renal clearance</td>
<td>Anti-arrhythmics drugs (quinidine, verapamil, amiodarone, propafenone)</td>
</tr>
<tr>
<td>Decreased gut absorption</td>
<td>Cholestyramine, sulphasalazine</td>
</tr>
<tr>
<td>Decreased conversion in gut to digoxin reduction products</td>
<td>Erythromycin, tetracycline (in some patients)</td>
</tr>
</tbody>
</table>

are commonly administered with digoxin, and dosing of the cardiac glycoside must be adjusted accordingly. These interactions can be regarded as those influencing drug absorption, metabolism and excretion (Table 1).

Digoxin toxicity

Vigilance for this important complication is important, especially with the widespread use of digoxin, commonly in elderly patients with concomitant co-morbidity, including renal impairment and heart failure.

Disturbances of cardiac impulse formation, conduction, or both are hallmarks of digoxin toxicity. Among the most common ECG manifestations are ectopic beats of atrioventricular, junctional or ventricular origin, first-degree atrioventricular block, an excessively slow ventricular rate response to atrial fibrillation, or an accelerated atrioventricular junctional pacemaker. These manifestations require only a dosage adjustment and monitoring as clinically appropriate. More severe manifestations include severe bradycardia and heart block; in cases where concomitant electrolyte abnormalities are present, malignant ventricular arrhythmias may occur.

In severe bradycardias causing haemodynamic compromise, temporary ventricular pacing may be needed. Potassium administration is often useful for atrial, atrioventricular, junctional, or ventricular ectopic rhythms, especially when the serum potassium is below the normal range, unless high-grade atrioventricular block is present. Magnesium administration may be useful in patients with atrial fibrillation and an accessory pathway in whom digoxin administration has facilitated a rapid pathway-mediated ventricular response.

Potentially life-threatening digoxin toxicity can be reversed by digoxin specific anti-sera. The smaller (molecular mass 50,000) Fab fragments have a larger volume of distribution, more rapid onset of action, and more rapid clearance, as well as reduced immunogenicity. Doses of Fab are calculated on the basis of a simple formula based on either the estimated dose of drug ingested or the total body digoxin burden and are administered intravenously in saline over 30 to 60 min. Nevertheless, the efficacy and cost-effectiveness of less than complete neutralizing doses of digoxin-specific Fab fragments for suspected or moderate cases of digoxin toxicity need further assessment.

Efficacy of digoxin in heart failure

There has been controversies surrounding the clinical efficacy of cardiac glycosides in the treatment of heart failure since the turn of the century. Over the past decade, the results of several randomized controlled trials support the use of digoxin when administered either alone or with vasodilators, to patients with heart failure due to predominant systolic ventricular dysfunction, even though patients are in sinus rhythm.

The PROVED (Prospective Randomized study of Ventricular failure and Efficacy of Digoxin) and RADIANCE (Randomized Assessment of Digoxin on inhibition of Angiotensin Converting Enzyme) trials were two prospective, multi-centre placebo-controlled ‘withdrawal’ trials that examined the effects of withdrawal of digoxin in patients with stable mild to moderate heart failure (that is, New York Heart Association class II and III) in normal sinus rhythm and systolic ventricular dysfunction (defined as a left ventricular ejection fraction of ≤35%). The target serum digoxin concentration in both studies during the baseline run-in phase was 0.7–2.0 ng/ml, with an average digoxin dose of 0.38 mg/day. When patients were randomly assigned to either continue active digoxin therapy or to withdraw from active therapy and receive a matching placebo, there was a significant worsening of heart failure symptoms in 40% of patients in the PROVED trial and in 28% of patients in the RADIANCE trial who received placebo, when compared with 20% and 6%, respectively, in patients who continued to receive active drug. Maximum treadmill exercise tolerance also declined significantly in patients withdrawn from digoxin in both trials, despite continuation of other medical therapies for heart failure, including ACE inhibitor therapy in the RADIANCE trial. However, none of these trials had the statistical power to detect an effect of digoxin therapy on the survival of patients with heart failure.

In the DIG (Digoxin Investigators’ Group) trial, patients with heart failure and sinus rhythm were
randomized to receive digoxin (3397 patients) or placebo (3403 patients), in addition to diuretics and ACE inhibitors, with a median dose of digoxin 0.25 mg/day and a mean follow-up period of 37 months. Patients were required to have current or past evidence of signs and symptoms of heart failure and a left ventricular ejection fraction of ≤45%. In a parallel, separate smaller study (988 patients) the effects in those with ejection fraction of >45% were studied. The primary end-point of the study was the effect of digitalis on total mortality; whilst secondary end-points included hospital admission for worsening heart failure or other causes, cardiovascular mortality, death due to worsening heart failure and (presumed) arrhythmia, and effects on quality of life. The DIG trial found that digoxin did not reduce overall mortality, but the number of hospital admissions and deaths due to worsening heart failure were significantly reduced by digoxin. However, there was a trend towards an increased incidence of presumed arrhythmic deaths, and deaths due to myocardial infarction tended to increase. The reduction in risk of worsening heart failure by digoxin was most pronounced in patients with a lower ejection fraction, but the reduction was not statistically significantly different between patients with relatively preserved and those with relatively impaired left ventricular function, thus allaying the concerns about the use of digoxin in patients with heart failure due to diastolic dysfunction.

Having established some benefits of digoxin in heart failure, many questions also arise. For example, how early should we initiate digoxin therapy in such patients? Does acute, short-term treatment with digoxin confer similar benefits to long-term, chronic treatment? In addition, should patients with very mild heart failure be treated with digoxin? For example, there is now some evidence that patients with left ventricular systolic dysfunction are at risk of clinical deterioration after digoxin withdrawal, despite only clinical evidence of mild congestive heart failure.43

Conclusions
We are still learning about a drug which has been in clinical use for the last 200 years, and there may still be much more to learn. Despite its common usage in Britain for rate control in atrial fibrillation, some authorities (especially in North America) have described digoxin as a drug ‘whose time has gone’, as beta-blockers and calcium antagonists (verapamil, diltiazem) are being regarded as being more efficient. Digoxin has recently been re-visited for its role in heart failure; while the value of digoxin in patients with heart failure who have atrial fibrilla-

References
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