

Digoxin

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Introduction

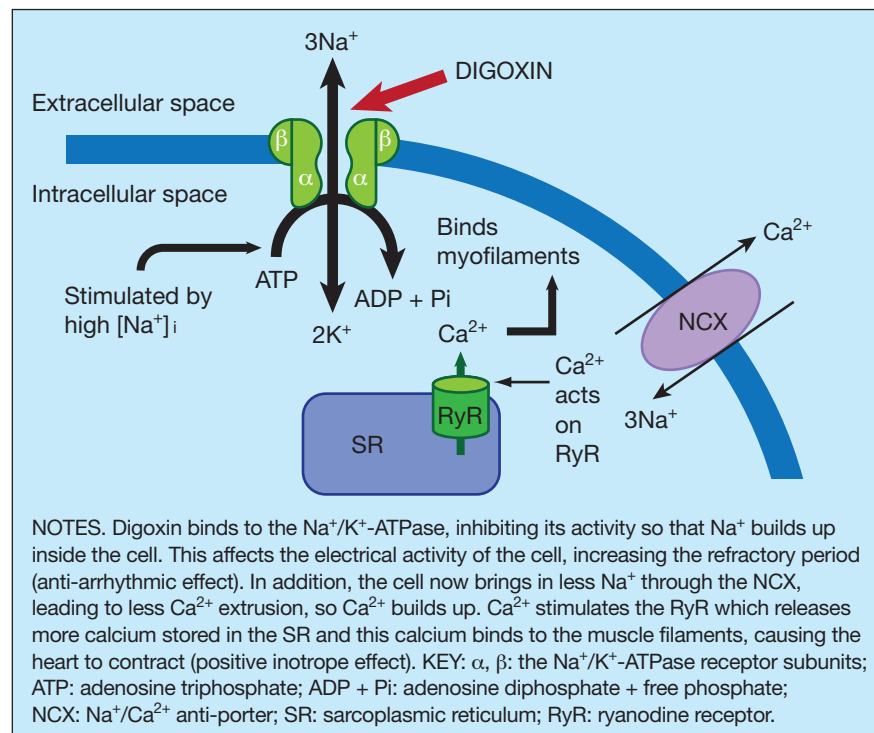
Digoxin has been used in clinical practice for four centuries. This cardiac glycoside, originally extracted from the foxglove, controls the ventricular response to the atrial rate and has a positive inotropic action. Patients with diabetes are at an increased risk of developing heart failure, and the prevalence of diabetes in patients with chronic heart failure is 20–30%.¹ Heart failure (HF) and atrial fibrillation (AF) often co-exist and in this setting digoxin is the first-choice agent. It is not the first-choice agent for patients with HF in sinus rhythm, or with AF and a fast ventricular response, but may be of therapeutic benefit for some patients.

Pharmacology

Figure 1 outlines the pharmacological action of digoxin. It contains an active aglycone steroid ring which inhibits Na^+/K^+ -adenosine triphosphatase (Na^+/K^+ -ATPase) in the cell membrane, altering the established resting membrane potential. Conduction is slowed and the refractory period increased. Intracellular $[\text{Na}^+]_i$ is increased which increases intracellular $[\text{Ca}^{2+}]_i$ by reduced extrusion through the $\text{Na}^+/\text{Ca}^{2+}$ ATP-independent anti-porter. Further calcium release results from stimulation of the ryanodine receptor (RyR) to release Ca^{2+} from the sarcoplasmic reticulum (SR). The increase in intracellular calcium has a positive inotropic effect.

Digoxin can convert atrial flutter into fibrillation by *shortening* the atrial refractory period, but prolonging the atrioventricular node (AVN) refractory period. It does this by releasing acetylcholine from the vagus nerve onto the sinoatrial node (SAN) and AVN (action on the paravertebral ganglion) causing 2:1 AVN block.

Figure 1. Pharmacological action of digoxin



Accumulatively, the faster atrial rate 'worsens' the AVN block (longer refractory state) leading to AV-dissociation and thus a safer ventricle rate. This pharmacological effect of digoxin causes problems if used in Wolff-Parkinson-White syndrome if the faster atrial rate is conducted through the uninhibited accessory pathway potentially leading to ventricular fibrillation (VF).

The half life ($t_{1/2}$) of digoxin is 24–48 hours with stable concentration achieved with daily dosing by five to 10 days. Serum digoxin levels are useful in the evaluation of toxicity, not clinical efficacy; therefore routine measurement is not required. Toxic concentrations are reached with lower doses in hypothyroidism, hypokalaemia or hypomagnesaemia. Concomitant administration of agents causing these disturbances, as

well as those that increase efficacious binding to Na^+/K^+ -ATPase (e.g. diuretics, β -agonists and carbenoxolone), will increase the likelihood of toxicity. Drug interactions can occur due to altered absorption (reduced by antacid, bile acid binding resins and tetracyclines) and renal elimination (usually 80%; reduced by quinidine, verapamil, amiodarone). Although 80% of digoxin is eliminated by renal filtration, tubular secretion and reabsorption have a role. Interestingly, a minimal amount is excreted after metabolism in bile and faeces but these routes can fully compensate in the absence of functioning kidneys.

Trials of safety and efficacy

In recent years, the clinical approach to managing AF has changed, and a number of studies have supported

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rate control rather than rhythm control. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)² trial included a range of rate-control strategies. This randomised multi-centre comparison which enrolled 4060 patients looked at the primary endpoint of total mortality in rate control *versus* rhythm control, and at secondary endpoints including evidence of cerebral ischaemia and quality of life. Digoxin was the most frequent first-choice for rate control in HF and digoxin or a β -blocker in patients without HF. Patients with diabetes were not excluded from the study but no details of numbers recruited or analysis were presented for this group. AFFIRM showed no difference between a rate or rhythm approach (mortality at five years, 21.3% *versus* 23.8%, respectively; hazard ratio 1.15; 95% CI 0.99–1.34; $p=0.08$).

The role of digoxin in heart failure when in sinus rhythm is less clear. The Digitalis Investigation Group (DIG) examined the effects of digoxin on overall mortality in patients with a left ventricular ejection fraction (LVEF) of 45% or less, with further data gathered on those with an LVEF greater than 45% (diastolic HF/preserved ejection fraction HF). In those with LVEF of 45% or less, 3397 patients in sinus rhythm were randomised to receive digoxin (mean daily dose 250 μ g) and 3403 to receive placebo. All randomised patients tended to be established on an ACE inhibitor and diuretic. Mortality was unaffected at 37 months (relative risk 0.99; 95% CI, 0.91–1.07; $p=0.80$) but digoxin reduced the rate of overall hospitalisation.³ The ancillary trial in parallel to the main DIG trial examined 988 HF patients with LVEF >45%, in sinus rhythm. They used a combined endpoint of HF hospitalisation and HF mortality in addition to assessing HF hospitalisation and cardiovascular mortality (the primary outcome in CHARM-Preserve, a major study of diastolic HF). Analyses were with an intention to treat and mean follow up was 37 months. The results showed that digoxin did not affect prognosis in ambulatory diastolic HF patients.

Specific evidence for use in diabetes

There are no studies which directly examine the use of digoxin in patients with diabetes. Some evidence exists from subgroup analyses. In the CHARM (Candesartan in Heart-Failure Assessment of Reduction in Mortality and Morbidity) post-hoc analyses, 7.8% (27.8 new cases per 1000 per year) of patients with heart failure were newly diagnosed with diabetes during follow up (median data collection 2.8 years) and, using multiple logistic regression, baseline digoxin therapy was one of the independent characteristics associated with incident diabetes (odds ratio 1.65; $p=0.022$). However, this did not translate into digoxin therapy being a predictor of developing diabetes.¹ Post-hoc analysis of the DIG data showed diabetes was an independent predictor of female patient all-cause mortality and hospitalisation.⁴ There are some minimal study evidence and case-data demonstrating that digoxin attenuates the effect of insulin and increases blood glucose concentration. Theoretically, this occurs in insulin-sensitive tissue where the Na^+/K^+ -ATPase is stimulated by insulin. Low intracellular $[\text{Na}^+]$ then stimulates glucose uptake by secondary active transport. It is suggested that digoxin inhibition of Na^+/K^+ -ATPase might lead to increased intracellular $[\text{Na}^+]$ and therefore reduced glucose uptake. However, the clinical relevance of these findings is not clear.

Renal function is an important determinant of digoxin dosage, so diabetic patients with renal impairment will require smaller doses.

Discussion

Rhythm-control strategies for patients with AF offer no advantage over rate-control strategies in terms of mortality or quality of life, and they are associated with a higher rate of hospitalisation, but exercise tolerance is greater with rhythm control. The therapeutic strategy in AF should therefore be individualised to patient needs. β -blockers achieve better control with exercise, and are first line in therapy in paroxysmal AF. Digoxin should be used as monotherapy in predominantly sedentary patients with permanent AF; however, it should be added

Key points

- Rhythm-control strategies for patients with atrial fibrillation, with or without heart failure, offer no clear survival advantage over rate-control strategies, and management should be based on patient needs with specialist cardiologist advice as required
- Digoxin should be used as first-line monotherapy in predominantly sedentary patients with permanent atrial fibrillation
- There is no evidence to suggest that treatment considerations for the use of digoxin should be different for patients with diabetes

in where monotherapy with rate-limiting calcium antagonists or β -blockers has been inadequate.

In heart failure and atrial fibrillation, a routine rate-control strategy is as effective as a rhythm-control strategy. Digoxin does not have an effect on mortality in sinus rhythm heart failure, regardless of the degree of systolic dysfunction, but reduces the overall rate of hospitalisation. There is no evidence to suggest that treatment considerations for the use of digoxin should be different for patients with diabetes.

For patients already on digoxin, care should be taken when prescribing other drugs, particularly in the acute setting – e.g. diuretics, tetracyclines – because of the potential for drug interactions resulting in digoxin toxicity.

Conflict of interest statement

There are no conflicts of interest.

References

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