



# THE USE OF DIGOXIN

The main indication for digoxin is permanent/persistent stable atrial fibrillation with a fast ventricular rate. The optimum resting ventricular rate is usually about 90/min, but this will depend upon the nature of the underlying heart disease (slower rates are desirable in mitral stenosis whilst faster ones may be appropriate in patients with poor left ventricular function). However, digoxin does not prevent exercise-induced tachycardia, and if there are symptoms (e.g. palpitation) during exercise, add a beta blocker or a rate limiting calcium channel blocker, such as diltiazem. <sup>1</sup> For patients whose ventricular rate does not slow with digoxin, amiodarone is an effective alternative.

The efficacy of digoxin in paroxysmal atrial fibrillation is less certain and controversial. However, since there is evidence that it does not prevent paroxysmal attacks and may even prolong attacks when they occur, it is better avoided. <sup>2</sup>

The value of digoxin in patients with heart failure in sinus rhythm is debatable. Although large randomized withdrawal studies after long-term therapy (PROVED <sup>3</sup> and RADIANCE <sup>4</sup>) showed that patients' heart failure and exercise tolerance deteriorated after withdrawal in about a quarter of cases, suggesting long-term benefit, there are other effective treatments for heart failure, including ACE inhibitors, beta blockers and spironolactone, all of which reduce mortality. Furthermore, the DIG study, a large prospective randomized trial, showed that digoxin had no effect on mortality and only led to a small reduction in the number of hospital admissions. Since digoxin is hard to use without avoiding toxicity, its minimal efficacy in heart failure in sinus rhythm does not justify its use as a first-line drug. It should be reserved for patients who do not respond fully to other therapy.

### Dosages

Use digoxin orally. Intravenous administration is rarely and intramuscular administration never justified. If possible, start with a loading dose of about 15 micrograms per kg of estimated lean body weight, given in three divided doses at 6 hour intervals. For example, you would give a 50 kg woman 750 (15 x 50) micrograms, in three doses of 250 micrograms each, 6 hours apart. If the ventricular rate does not slow satisfactorily and there is no evidence of toxicity, try

another 5 micrograms/kg (in this case another 250 micrograms). If this is ineffective try another drug. If it is effective, give a maintenance dose based on renal function:

Creatinine clearance (ml/min)	Daily maintenance dose as a fraction of the effective loading dose
100	1/3
50	1/4
25	1/5
10	1/6
0	1/7

Treatment with a loading dose in this way requires careful monitoring during the early stages. If that is not possible, give a regular maintenance dose from the start. That means a maintenance dose of 5 micrograms per kg in a patient with normal renal function (250 micrograms/day in the patient discussed above). However, it will take at least a week for this dosage to build up to an effective therapeutic amount in the body (longer in a patient with renal impairment), so this is a less ideal method of treatment.

### Adverse effects

The adverse effects of digoxin can be either cardiac or non-cardiac. The non-cardiac adverse effects include nausea, vomiting, anorexia, and (particularly in elderly people) diarrhoea. Confusion and delirium can occur occasionally. Colour vision abnormalities are rare. Digoxin can cause any kind of cardiac rhythm disturbance, especially heart block and ectopic arrhythmias, particularly in combination. If you suspect toxicity, withdraw the digoxin, and if there is evidence of potassium depletion give potassium supplements. Severe toxicity needs hospital admission for the administration of antidigoxin antibody fragments.

### Factors that increase the risk of toxicity

Renal insufficiency causes retention of digoxin, and dosages should be reduced. This is particularly important in elderly people, in whom renal function becomes progressively impaired with age.

Potassium depletion increases the response of the tissues to digoxin and can cause digoxin toxicity.

Common causes of potassium depletion include diuretic therapy and acute vomiting or diarrhoea.

Do not use digoxin in patients with active thyroid disease. Patients with hyperthyroidism may not respond well but can develop toxicity if the dosage is increased. Patients with hypothyroidism are more sensitive to the effects of digoxin and it can be very hard to find the correct dosage.

#### Drug interactions

Prevent potassium depletion in patients taking diuretics by using a potassium-sparing diuretic and monitor the plasma potassium concentration regularly. Remember that ACE inhibitors and angiotensin receptor antagonists can cause potassium retention.

Digoxin is excreted by a transporter in the kidney called P-glycoprotein. Drugs that inhibit this protein can cause variable degrees of digoxin retention. The most important of these is amiodarone; it is usually best to withdraw digoxin when using amiodarone. Other drugs that can interact in this way include diltiazem, verapamil, itraconazole, quinidine, and spironolactone. There is usually no need to withhold digoxin when these drugs are added, but plasma concentration

monitoring will help to avoid toxicity.

In about 10 per cent of patients digoxin is metabolized in the gut by intestinal bacteria, mainly *Eubacterium glenum*. The antibiotics erythromycin, clarithromycin, and tetracycline inhibit this breakdown and so increase the systemic availability of digoxin.

#### Monitoring therapy

The ventricular rate is the best measure of the response in atrial fibrillation. The beneficial effect of digoxin in heart failure in sinus rhythm is too small to detect clinical changes, but symptoms may improve.

Plasma concentration measurement can be useful in individualizing therapy during the early stages of treatment, for detecting poor patient compliance with therapy, and for diagnosing toxicity. Aim for a target plasma concentration of 1.0-1.5 nmol/l but concentrations up to 2 nmol/l may be required in patients with atrial fibrillation. Concentrations above 2 nmol/l usually suggest toxicity. However, if you suspect digoxin toxicity, first measure the plasma potassium concentration; if there is evidence of potassium depletion, withhold digoxin, no matter what the plasma digoxin concentration.

## Further Reading

1. Aronson JK, Hardman M, Reynolds DJM. ABC of monitoring drug therapy. London: BMJ Publishing Group, 1993.
2. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *New Engl J Med* 1997; 336: 525-33.
3. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, van Voorhees L, Gourley LA, Jolly MK, for the RADIANCE study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *New Engl J Med* 1993; 329: 1-7.
4. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. *J Am Coll Cardiol* 1993; 22: 955-62.