Digoxin and the Cardiac Glycosides

Cardiac glycosides include digoxin, digitoxin, digitalis and ouabain. Of these, only digoxin is in regular use in the UK. Prescribing digoxin is not difficult, providing certain principles are followed.

How does digoxin work?

Digoxin acts by inhibiting cell membrane sodium/potassium ATPase which leads to reversal of the usual sodium/calcium exchange. An increased intracellular calcium level results which, in myocardial muscle, has the effect of enhancing the strength of contraction (positive inotropism). It also affects the electrical physiology of the heart, blocking atroventricular (AV) conduction and reducing the heart rate by enhancing vagal nerve activity (negative chronotropy).

In what conditions should digoxin be considered?

Atrial fibrillation (AF)
The principal indication is permanent/persistent AF with a fast ventricular rate - although it is not the preferred first-line medication (especially as digoxin prevents the normal rise in heart rate associated with exertion). Digoxin is ineffective in converting recent-onset AF to sinus rhythm and it is also contra-indicated in pre-excited AF [1]. Digoxin has fallen out of favour due to studies reporting increases in all cause mortality when given in AF - especially if no heart failure is present [2]. It is still, however, used as monotherapy primarily in patients who cannot tolerate the alternatives and in severe heart failure. It is also used in the acute setting, particularly where AF occurs in sepsis and is associated with hypotension. The target should be a resting ventricular rate of approximately 90/minute.

Alternatives include beta-blockers or rate-limiting calcium-channel blockers which are the preferred choices and are more effective for monotherapy in patients likely to undergo exertion [1].

Supraventricular tachycardia
Digoxin is most commonly used in this situation in children with congenital heart disease. It is given intravenously in the acute situation to slow the heart rate.

Heart failure [4]
National Institute for Health and Care Excellence (NICE) guidance suggests that digoxin should be used as first-line in patients with AF who also have co-existing heart failure. In all other cases where heart failure is due to left ventricular dysfunction it should be reserved for patients in whom the condition has worsened despite the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and diuretic therapy.

How is the initial dosage calculated?

- For patients with AF and atrial flutter, digoxin works best when a high dose is given as an initial loading dose (rapid digitalisation).
- A loading dose should be given of 15 micrograms/kg of lean body weight. For a woman with a lean body weight of 50 kg this would work out at a total dose of 15 x 50 = 750 micrograms. Lean body weight is defined as total body mass minus fat mass. There are a number of methods for determining this but where it is clinically significant the simplest method in primary care is the use of skin calipers [5].
- The range is usually 750-1500 micrograms in over a 24-hour period. It is commonly given orally and rarely intravenously. The dose is given once daily except in elderly patients in whom it should be given in divided doses over a six-hourly period. If the ventricular rate does not reduce to the desired target, an additional dose of 5 micrograms/kg can be given, providing there are no symptoms or signs of toxicity (see under 'Monitoring', below). If the rate does not come down after a further dose, another drug should be given.
- Slow loading may be more appropriate, depending on the clinical state of the patient and the urgency of the condition. It can be achieved by giving 250 to 750 micrograms daily for one week followed by an appropriate maintenance dose. A clinical response should be seen within one week.
- In the rare patient with AF or atrial flutter who requires emergency digitalisation, intravenous infusion can be used. The dose is 0.75-1 mg given as two doses six hours apart. Continued maintenance dose by mouth is given on the following day.
- Heart failure (patients in sinus rhythm) should be given 62.5-125 micrograms by mouth once daily. No loading dose is required.

How should the maintenance dose be calculated?

The maintenance dose is calculated as a fraction of the effective loading dose, adjusted for renal function.
<table>
<thead>
<tr>
<th>Creatinine clearance (mL/minute)</th>
<th>Daily maintenance dose as a fraction of the effective loading dose</th>
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<tbody>
<tr>
<td>100</td>
<td>1/3</td>
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<tr>
<td>50</td>
<td>1/4</td>
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<tr>
<td>25</td>
<td>1/5</td>
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<td>10</td>
<td>1/6</td>
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<td>0</td>
<td>1/7</td>
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**Monitoring**

Monitoring is important, both to ensure that the correct dosage is being given and also that factors which might provoke toxicity - eg, renal dysfunction and hypokalaemia - are not developing. Features suggestive of toxicity include nausea, vomiting, diarrhoea, dyspnoea, confusion, dizziness, headache, blurred vision and diplopia. See the British National Formulary (BNF) for the full list.[6]

U&Es should be monitored. In stable patients this may be done annually but if there is any change in dosage or clinical status, more regular monitoring should be performed.

The best monitor of response to treatment in AF is ventricular rate. Plasma concentrations can, however, be helpful when initiating therapy, checking compliance or detecting toxicity. A target range of 1.0-1.5 nmol/L should be aimed for but concentrations of 2 nmol/L may be required in AF. Levels above 2 nmol/L suggest toxicity. Plasma potassium should be measured in all cases of suspected toxicity. If hypokalaemia is evident, the drug should be withheld irrespective of the digoxin level.

For details of contra-indications and interactions, see the BNF[6].

**Further reading & references**

4. Definition of lean body mass; MedicineNet.com
5. British National Formulary (BNF); NICE Evidence Services (UK access only)

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