Digoxin monitoring: why, when & how

A recent audit of one hundred consecutive digoxin therapeutic drug monitoring (TDM) requests at Christchurch hospital demonstrated a significant number of deficiencies. This bulletin summarises digoxin therapy and provides advice on TDM.

Why measure digoxin concentrations?

The audit revealed that in approximately 50% of requests, digoxin TDM was performed with no clear indication.

TDM is designed to aid clinical decisions and not to be the sole guide. To use digoxin TDM appropriately requires knowledge of what the therapeutic range represents and its limitations.

The therapeutic range of 1.0 to 2.5 nmol/L is predominantly based on the low therapeutic index of digoxin. Toxicity increases significantly with concentrations over 2.5 nmol/L and is almost invariable in those with concentrations greater than 3.8 nmol/L.

The validity of the therapeutic range in terms of efficacy is less clear. Studies have not demonstrated a relationship between digoxin concentration and heart rate in chronic atrial fibrillation. However, in individual patients there may be an association, and therefore TDM may be useful to determine whether the dose can be safely increased without resulting toxicity. In heart failure the relationship is even less clear, with recent literature suggesting that lower concentrations are as efficacious as higher concentrations, although a number of methodological problems with the studies referenced give uncertainty to this.

Indications for measuring digoxin concentrations:

- Confirmation of toxicity. Symptoms include nausea, vomiting, diarrhoea, abdominal pain, confusion, dizziness, agitation, arrhythmias, heart block and various visual symptoms. The likelihood of toxicity is increased if the prescribed dose has not taken into account the patient’s creatinine clearance or drug interactions (Table 1).
- Assessing compliance.
- Therapeutic failure.

Table 1: Drug interactions

<table>
<thead>
<tr>
<th>Increased digoxin concentrations (usually 30-100%):</th>
<th>Decreased digoxin concentrations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>spironolactone, amiloride, triamterene, quinidine, amiodarone, verapamil, macrolide antibiotics.</td>
<td>rifampicin, liquid antacids.</td>
</tr>
</tbody>
</table>

When to measure the concentration

The audit revealed that one third of samples are taken too soon after a digoxin dose and 20% did not reflect a steady-state situation.

Digoxin concentrations should be measured at least eight hours following an oral dose of digoxin and ideally when they have reached steady-state. To understand the reasons for this requires some understanding of the pharmacokinetic profile of digoxin.

Post-distribution concentration. Digoxin is usually well absorbed with peak concentrations occurring within 1 hour. A large volume of distribution (4-7L/kg) reflects that digoxin concentrates in the tissues (the active site). The distribution from serum to tissue takes at least 8 hours (see graph). Samples taken prior to 8 hours will give a false indication of elevated tissue concentrations, and inappropriate dose reduction may result.

Steady-state. Digoxin elimination is primarily renal (t1/2 0.6-0.9), and depends upon glomerular filtration and P-glycoprotein mediated active tubular secretion. A long t1/2 of at least 30 h (in normal renal function) results in steady-state concentrations taking at least 5 days to be achieved. In the elderly and in patients with renal impairment, elimination is diminished, with a half-life of up to several days. Steady-state may take a few weeks to achieve. Concentrations taken before steady-state is reached may provide a falsely low result, and inappropriate dose increases may result.

Graph: Digoxin concentrations following an oral dose

How to adjust the dose

Serum digoxin concentrations need to be interpreted within the clinical context.

Toxicity is generally a clinical diagnosis supported by an elevated digoxin concentration. However, toxicity is not excluded by concentrations within the therapeutic range. Conversely, an elevated concentration does not automatically imply toxicity, although the benefit of a higher concentration is questionable. Other factors (Table 2) that affect tissue sensitivity to digoxin and alter the therapeutic index need to be considered.

The period of time that digoxin should be withheld after toxicity depends upon how high the concentration is, and the half-life in that patient. In a patient with normal renal function and a concentration of 3.0 nmol/L, the digoxin should be withheld for T-2 days before restarting at the appropriately altered dose. In renal impairment with a prolonged t1/2, several days of withholding may be required.

Dose-adjustment for therapeutic failure should only be performed following a digoxin concentration measured at steady-state. A change in dose will give a proportional change in digoxin concentration eg, doubling the dose will double the digoxin concentration and halving the dose will halve the concentration (assuming the pharmacokinetics remain unchanged).

In situations where there is changing renal function then the adjustment can be estimated by calculating the change in creatinine clearance using the Cockcroft & Gault formula. For example, a halving of the patient’s renal function from baseline means that only half of the initial dose will be required to maintain the same steady-state concentration.

Table 2: Factors altering digoxin sensitivity & likelihood of toxicity

<table>
<thead>
<tr>
<th>Increased Sensitivity</th>
<th>Decreased Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalaemia</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypoxia/acidosis</td>
<td>Neonates</td>
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</tbody>
</table>