Aims of the Bulletin

- To increase understanding of dose regimes and the role of therapeutic drug monitoring.
- To raise awareness of factors which contribute to digoxin toxicity.
- To give guidelines on the management of digoxin toxicity.

Contents

1) Factors affecting choice of digoxin dose.
2) Administration – loading and maintenance doses.
3) Therapeutic drug monitoring – when to take levels and what do they mean?
5) Digibind – what is it? How to use it.
6) Drug interactions that matter.

1) Factors affecting choice of digoxin dose

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Increasing age</td>
<td>Reduced digoxin clearance</td>
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<tr>
<td>Reduced renal function</td>
<td>Reduced digoxin clearance</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>Increased sensitivity of myocardium to digoxin</td>
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<tr>
<td>Hypomagnesaemia</td>
<td>Increased sensitivity of myocardium to digoxin</td>
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<tr>
<td>Marked hypercalcaemia</td>
<td>Increased sensitivity of myocardium to digoxin</td>
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<tr>
<td>Hypothyroidism</td>
<td>Lower digoxin doses may be required</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Increased digoxin doses may be required due to relative digoxin resistance</td>
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<tr>
<td>Severe respiratory disease</td>
<td>Increased sensitivity of myocardium to digoxin</td>
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<tr>
<td>Exposure to cardiac glycosides in the previous two weeks</td>
<td>Lower digoxin doses may be required</td>
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<tr>
<td>Reduced lean body mass (e.g. elderly)</td>
<td>Lower digoxin doses may be required</td>
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<tr>
<td>Cardiovascular disease</td>
<td>Increased sensitivity to digoxin</td>
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<tr>
<td>Hypoxia</td>
<td>Increased digoxin effects</td>
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<tr>
<td>Patients with small bowel resections</td>
<td>May need an increased digoxin dose</td>
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<tr>
<td>Other medication</td>
<td>Consider potential for interaction.</td>
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</table>
2) Administration – loading + maintenance doses

For a rapid effect, a loading dose should be given (otherwise it may take 7-14 days to reach steady state).
Loading doses do not need to be reduced for patients with impaired renal function – only the maintenance dose needs amendment.

**Oral loading (adults) – preferred if patient is alert and able to swallow:**
Rapid – 750mcg to 1500mcg as a single dose (or preferably in divided doses given 6 hours apart if dose is near top of the range).
   *Example: 500mcg stat, followed by 500mcg 6 hours later*
Slow (e.g. for outpatients) – 250mcg once or twice a day for one week.

**Intravenous loading (adults) – for rapid control:**
Dose: 500mcg – 1000mcg as a single IV infusion over at least 2 hours or given in divided doses as IV infusions over 20 minutes.
   *Example: 500mcg IV over 20 mins, 6 hours later followed by 250mcg IV over 20 mins*

**Method of IV administration:**
The required dose is added to 50-100ml sodium chloride 0.9% or glucose 5%.
Rapid IV injection may cause vasoconstriction and transient hypertension.
There is no need for continuous ECG monitoring during IV administration.

**Oral maintenance dose (adults):**
Usually 125mcg to 250mcg daily (range 62.5mcg to 500mcg daily).
Heart rate should be maintained at greater than 60 beats per minute.

**Alternatives for patients unable to take their usual oral maintenance dose:**
Digoxin liquid – same dose as for tablets (bioavailability for the preparations is similar).
Digoxin by IV infusion – ideally dose should be reduced by one third, but in practice this is not done – best to give over 2 hours.

**Do not give by IM/SC injection** - IM injection is painful and tissue damage may occur, SC injection will cause intense local irritation.

3) Therapeutic Drug Monitoring – when to take levels and what do they mean?

<table>
<thead>
<tr>
<th>Blood levels are helpful when:</th>
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<tr>
<td>• poor compliance is suspected,</td>
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<td>• response to treatment is poor,</td>
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<tr>
<td>• there is a deterioration in response to treatment,</td>
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<tr>
<td>• renal function is fluctuating,</td>
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<tr>
<td>• drugs that interact are co-prescribed,</td>
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<tr>
<td>• confirmation of clinical toxicity is needed,</td>
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<tr>
<td>• it is unknown if cardiac glycosides have been taken in previous 2 weeks.</td>
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</table>

Samples must be taken **at least 6 hours after the last dose** and should be taken only when steady state is likely to have been achieved (when no loading dose is given, this may take 7 days in patients with a normal renal function and 14 days for elderly patients).
Falsely elevated plasma digoxin levels may be seen in certain patients who have digoxin-like substances in their serum (patients with renal or hepatic dysfunction, pregnant women and neonates). Approximately 90% of adults with proven digoxin toxicity have a plasma digoxin level greater than 2.6nmol/l.

### 4) Digoxin toxicity – signs, symptoms and treatment.

**Signs and symptoms of digoxin toxicity**
- Cardiac – almost any arrhythmia, heart block and heart failure.
- Neurological – headache, facial pain, fatigue, weakness, general malaise, dizziness, drowsiness, disorientation, mental confusion, bad dreams, delirium, psychoses and hallucinations.
- Gastrointestinal – anorexia, nausea, vomiting and abdominal pain.
- Visual – blurred and/or yellow vision.

**Treatment of digoxin toxicity** – Consider contacting the cardiology team or the Poisons Information Service (phone number inside front cover of BNF) for advice.

1. Stop digoxin.
2. Check serum potassium, magnesium, urea, creatinine and digoxin levels (for long term digoxin administration ensure blood sample is taken at least 6 hours after the last digoxin dose was given otherwise the result will be falsely elevated).
3. Correct the serum potassium (use oral or IV supplementation for hypokalaemia, use IV insulin + glucose for hyperkalaemia – avoid calcium)
5. Correct metabolic acidosis with IV sodium bicarbonate.
6. Monitor pulse, blood pressure and cardiac rhythm.
7. Monitor ECG and treat arrhythmias as appropriate:
   - Bradycardia and AV block – use atropine.
   - Ventricular arrhythmias – use IV magnesium.
   - Severe life threatening arrhythmias resistant to other measures – Digibind ® may be appropriate.

### 5) Digibind ® - What is it? How to use it.

**When should it be used?**
ONLY for clinically significant digoxin toxicity – the advice of a Consultant should be sought before prescribing – it is not appropriate for all patients.

**What is it?**
This contains digoxin specific antibody fragments which have a higher affinity for digoxin than the receptor in the body.

**Dose calculation for the treatment of toxicity occurring during chronic therapy for adults > 20kg (if for acute overdose, see package insert):**
The recommended dose is 6 vials if no steady state concentration is available. If the steady state serum concentration is known, the number of vials can be calculated using the following equation:

\[
\text{No of vials} = \frac{\text{serum digoxin level (nmol/l)} \times \text{patient’s weight (kg)}}{100} \times 0.781
\]

The dose should be rounded up to the next whole vial.
Administration
Patients should have continuous ECG monitoring during the administration of Digibind® and for 24 hours after. It is normally stored in the fridge on the cardiac ward. Each vial should be reconstituted with 4ml water for injections and mixed gently. The solution should be diluted further with a convenient volume of sodium chloride 0.9% and be administered by IV infusion over 30 minutes through a 0.22 micron filter. If cardiac arrest is thought to be imminent, it can be given as an IV bolus.

Onset of action
After 30 minutes there should be an improvement in the signs and symptoms of digoxin intoxication.

Warnings
Significant hypokalaemia may occur after administration of Digibind®. Digoxin levels taken after the administration of Digibind® are likely to be raised and are meaningless as this reflects digoxin that is bound to the antibody fragments.

6) Drug interactions that matter.

Significant Drug Interactions (require amendment of digoxin dose)
- Amiodarone (halve digoxin dose when co-prescribed)
- Itraconazole (digoxin dose likely to need reduction during co-prescription)
- Propafenone (digoxin dose likely to need reduction during co-prescription)
- Quinidine (halve digoxin dose when co-prescribed)
- Verapamil (halve digoxin dose when co-prescribed)

Other Drug Interactions (advice is to monitor concurrent use carefully)
- Drugs which may reduce plasma digoxin levels: acarbose, antacids (separate administration by 1-2 hours), cytotoxics (intestinal damage may reduce absorption – advice is to change tabs to liquid), cholestyramine (separate time of administration), metoclopramide (advice is to change tabs to liquid), penicillamine, phenytoin, rifampicin, St Johns Wort (CSM advice is to avoid concurrent use) and sulfasalazine.
- Drugs which may increase plasma digoxin levels: atorvastatin (at high dose only), benzodiazepines (particularly alprazolam), captopril (other ACE inhibitors not implicated), chloroquine, ciclosporin, co-trimoxazole, diltiazem, etoricoxib, hydroxychloroquine, telmisartan (other angiotensin II antagonists not implicated), macrolide antibiotics (azithromycin, clarithromycin, erythromycin), nifedipine, NSAIDs, prazosin, propantheline (advice is to change tabs to liquid), quinine, rabeprazole, spironolactone, trimethoprim and trazodone.
- Drugs which may cause hypokalaemia: amphotericin, beta-agonists (such as salbutamol), corticosteroids, potassium depleting diuretics (such as acetazolamide, bendroflumethiazide, bumetanide, furosemide and indapamide).
- Drugs which may cause bradycardia such as beta-blockers, methyldopa and tizanidine.

This information is issued on the understanding that it is the best available from the resources at our disposal at the date of issue. Further information may be obtained from:
Medicines Information at GRH (tel 08454 226108 or internal extension 6108)
Medicines Information at CGH (tel 08454 223030 or internal extension 3030)