DIGOXIN

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The plasma digoxin concentration that will result from a given dose of the drug can be predicted at best with only 34% accuracy, although knowledge of a previous concentration improves the ability to predict subsequent concentrations. In outpatients taking a fixed daily dosage, a steady state plasma digoxin concentrations vary widely (between 0.5 and 3.5 nmol/l). This means that if a target plasma digoxin concentration is desirable measuring the concentration may be useful in tailoring dosages to individual requirements.

In this article we apply to digoxin the criteria (described in the previous article on measuring plasma drug concentrations) which must be fulfilled in part or in full before the measurement of its plasma concentration can be considered worth while.

Criteria for measurement

1. Is there difficulty in interpreting clinical evidence of the therapeutic or toxic effects?

In patients with atrial fibrillation the slowing of the ventricular rate is usually a good guide to the therapeutic effect of digoxin. However, in patients with congestive cardiac failure with sinus rhythm who are taking digoxin for its positive inotropic effect there is no easily measurable end point by which to assess the therapeutic response. Furthermore, digoxin toxicity can be difficult to diagnose because anorexia, nausea and vomiting, mental confusion, and cardiac arrhythmias may all be signs or symptoms of both congestive cardiac failure and digitalis toxicity. Thus measuring the plasma digoxin concentration will allow the dosage to be increased within safe limits in order to ensure, firstly, that an adequate response to treatment is not missed because the dose is suboptimal and, secondly, that toxicity does not occur because of too large a dose. Of course this assumes that there is a good relation between the plasma concentration of digoxin and its therapeutic or toxic effects.

2. Is there a good relation between the plasma concentration and its therapeutic or toxic effects?

In the case of atrial fibrillation there is good evidence that increasing the concentration of digoxin within the therapeutic range produces an increase in its effect of slowing the ventricular rate. In patients with sinus rhythm a relation between the plasma concentration of digoxin and its therapeutic effect has not been clearly established. Generally a satisfactory therapeutic response is most likely to be achieved when plasma digoxin concentrations are between 1.0 nmol/l and 2.6 or 3.8 nmol/l. These limits are based, at least in part, on observations outside this range: the risk of digoxin toxicity increases at concentrations above 2.6 nmol/l and is almost invariable at concentrations greater than 3.8 nmol/l, and it is difficult to detect any effect of digoxin when the plasma concentration is below 1.0 nmol/l. Within the range 1.0 to 3.8 nmol/l there is some evidence of dose responsiveness.

Although concentration correlates well with some measurable actions of digoxin on the heart, such as changes in systolic time intervals and changes in the electrocardiographic configuration (shortened PR interval, prolonged QTc interval, T wave depression and inversion), these changes are difficult to interpret in terms of the therapeutic outcome.
**Therapeutic range**
- Below 1 nmol/l a therapeutic effect is unlikely.
- Above 3.8 nmol/l the risk of toxicity increases considerably.
- Between 1 and 3.8 nmol/l a beneficial effect with a low risk of toxicity is likely.

Findings show a significant difference between plasma digoxin concentrations in toxic and non-toxic patients. However, as there is an overlap in the region between about 2 and 3.8 nmol/l diagnosis cannot be based on a patient’s plasma concentration alone.

<table>
<thead>
<tr>
<th>Plasma digoxin concentration (nmol/l)</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>0%</td>
</tr>
<tr>
<td>1 - 2</td>
<td>5%</td>
</tr>
<tr>
<td>2 - 3</td>
<td>10%</td>
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<td>3 - 4</td>
<td>20%</td>
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<td>4 - 5</td>
<td>30%</td>
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<td>5 - 6</td>
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<td>6 - 7</td>
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<td>9 - 10</td>
<td>80%</td>
</tr>
<tr>
<td>10 - 11</td>
<td>90%</td>
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<tr>
<td>11 - 12</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Measurement techniques**

All routine laboratories use immunoassay to measure plasma digoxin concentrations, and most use radioimmunoassay with digoxin antibody and an iodine-125 digoxin conjugate as a tracer. This is available in a kit and is relatively easy to use. The problem, as with all immunoassays, is that the antibody may cross react with other compounds. In this case examples include steroid hormones such as cortisol and drugs such as spironolactone. There is also evidence that the serum from neonates, pregnant women, and patients with chronic renal failure and essential hypertension may cross react with digoxin antibody — so called endogenous digitalis-like immunoreactivity. Some antibodies are more susceptible to cross reaction than others.

Most studies have shown a significant difference between the mean plasma digoxin concentration in groups of patients with toxicity and the mean concentration in groups without toxicity. The chief problem lies in making the diagnosis of digoxin toxicity in the individual patient. There is no doubt that the plasma concentration on its own is not always sufficient in deciding whether or not a patient has digoxin toxicity. The decision can be made only by considering the plasma digoxin concentration in the light of other clinical and biochemical information. Toxicity is likely when:
- The plasma digoxin concentration is greater than 3.8 nmol/l.
- The plasma digoxin concentration is less than 3.8 nmol/l and the plasma potassium concentration is less than 3.5 mmol/l.
- The plasma digoxin concentration is less than 3.8 nmol/l and there are any two of the following:
  - Plasma potassium >5 mmol/l
  - Plasma creatinine >150 µmol/l
  - Age >60 years
  - Daily maintenance dose >6 μg/kg (for example, 375 µg for a 60 kg patient)

Thus in a patient suspected of having toxicity the plasma potassium and digoxin concentrations and any factors which may alter the patient’s sensitivity to digoxin should be considered. If these all support the diagnosis of toxicity the digoxin should be stopped. If the diagnosis is still in doubt the patient should be carefully observed while continuing to take digoxin, but the situation must be reviewed and digoxin should be stopped if necessary. It is certainly better to withhold digoxin from a patient who does not have toxicity than to continue treatment in a patient who does.

For children over 1 year of age the same plasma concentrations are associated with toxicity as in adults. In infants and neonates, however, there is no clear cut pattern and plasma digoxin concentrations can be difficult to interpret.

**Is digoxin metabolised to active metabolites?**

Most patients metabolise less than 20% of digoxin, and so active metabolites are relatively unimportant. However, about 10% of patients metabolise up to 55%, both by hydrolysis to digoxigenin and to its bisdigtotoxides and monodigitotoxides; all of which have pharmacological activity, and by reduction to dihydrodigoxin, which is relatively inactive. This conversion is thought to occur in the bowel through an effect of gut bacteria, and in those patients in whom it occurs digoxin metabolism may be reduced by antibiotics such as erythromycin and tetracyclines.

In theory, if digoxin was assayed by measuring the pharmacological activity of all the components (both digoxin and its metabolites) the variation in digoxin would not be a problem. But the types of immunoassay routinely used do not necessarily measure all the metabolites, and in certain cases might give a spuriously low plasma concentration of active cardiac glycosides. This may explain some cases of digoxin toxicity in patients with plasma concentrations in the therapeutic range.
Factors affecting concentration

Factors which can increase the plasma digoxin concentration for a given dosage of digoxin include:
- Increased absorption due to change of formulation
- Impaired excretion — for example, impairment of renal function
- Drug interactions — for example, verapamil, quinidine, and amiodarone
- Impaired metabolism by antibiotics in people in whom significant metabolism of digoxin occurs in the gut

Factors which can alter the plasma digoxin concentration when the dosage is kept constant include altered absorption, altered excretion by the kidney, and drug interactions. For example, if renal function is impaired digoxin will be retained and the plasma digoxin concentration will increase without a change in dosage. Similarly, if another drug reduces the rate of elimination of digoxin (such as verapamil, quinidine, or amiodarone) the plasma digoxin concentration will increase.

Knowing the plasma digoxin concentration alone is not sufficient for optimal treatment. Several factors change the tissue response to digoxin and must be taken into consideration when interpreting plasma concentrations.

**Electrolyte disturbances** — Hypokalaemia is the most important and commonest factor which increases the sensitivity of the tissues to digoxin. A reduction in plasma potassium concentration from 3.5 to 3.0 mmol/l is accompanied by an increase in sensitivity to digoxin of about 50%. This is such an important factor that the plasma potassium concentration should always be measured with the plasma digoxin concentration. If the potassium concentration is low digoxin toxicity should be assumed without waiting for the plasma digoxin measurement. Hypercalcaemia and hypomagnesaemia may also be associated with increased tissue sensitivity to digoxin, but the available data are more difficult to interpret.

**Thyroid disease** — Hypothyroidism increases tissue sensitivity and hyperthyroidism decreases it. This makes interpretation of the plasma digoxin concentration very difficult in patients with thyroid disease.

**Age** — Elderly people may be more sensitive to digoxin’s effects, possibly because of reduced activity of Na’/K’ ATPase. However, current dosages and therapeutic guidelines for plasma concentration are mostly based on studies in elderly people.

Factors affecting interpretation

**Factors which increase tissue sensitivity to digoxin include:**
- Hypokalaemia (for example, due to diuretics)
- Hypercalcaemia
- Hypothyroidism
- Hypoxia and acidosis

**Factors which decrease tissue sensitivity to digoxin include:**
- Hyperkalaemia
- Hypocalcaemia
- Hyperthyroidism
- Neonates

Use of plasma measurements

Case history: problems associated with renal failure
A 55 year old man with chronic renal failure (creatinine clearance 50 ml/min) and hypertension was admitted with heart failure. He was found to have rapid atrial fibrillation with a ventricular rate of 170 beats/min. After a loading dose of 500 μg of digoxin his ventricular rate fell to 120 beats/min. With a maintenance dose of 125 mg daily it was still 120 beats/min. His steady state plasma digoxin concentration was 1.6 nmol/l. His daily digoxin dosage was increased by 62.5 μg (60%), which slowed the ventricular rate to 95 beats/min and his plasma digoxin concentration rose predictably to 2.4 nmol/l.

Conclusion
Giving the appropriate dosage of digoxin for the degree of renal impairment did not control the patient’s fibrillation. Knowing the plasma digoxin concentration allowed the digoxin dosage to be increased with minimum risk of toxicity.

If the steady state plasma digoxin concentration is known the change in dosage required to change the plasma digoxin concentration by a given amount can be calculated. A given percentage increase in the digoxin dosage will result in the same percentage increase in the steady state plasma concentration. For example, if a patient is taking 250 μg digoxin daily and has a steady state plasma digoxin concentration of 1.2 nmol/l, a daily dosage of 375 (250+125) μg will result in a plasma concentration of 1.8 (1.2+0.6) nmol/l. Thus we can calculate whether a given dosage increase will result in a plasma concentration within or above the therapeutic range.

In practice it is best to aim for a plasma digoxin concentration of 1.0-2.0 nmol/l in the first instance, raising the target carefully to a maximum of 3.0 nmol/l if a therapeutic response is not achieved.
Timing of measurements

There are two aspects to be considered in the timing of blood sampling for plasma digoxin concentrations.

(1) The time after a dose
The plasma digoxin concentration peaks at about one hour after the dose and is at a minimum (trough concentration) just before the next dose. At steady state the logarithmic mean of these measurements is the average steady state concentration, which occurs at about 11 hours after the dose. In practice, the blood sample should be taken at least six hours and preferably 12 hours after the previous dose. This can cause problems in the clinic or practice if the dose of digoxin has been taken in the morning, and patients should therefore be advised to take their digoxin in the evening, as the blood sample may then be taken at any time the next day.

(2) The time it takes during repeated dosage to reach steady state
Measuring the plasma digoxin concentration before a steady state concentration is reached will underestimate the steady state concentration. For example, if a patient takes a daily maintenance dose of digoxin without an initial loading dose it will take about five half lives of digoxin before a steady state is reached. Thus, assuming the patient has normal renal function, it will take \(5 \times 40\) hours (eight days) to reach a steady state. Of course it may be necessary to measure the plasma digoxin concentration before a steady state is reached if there are concerns about the possibility of digoxin toxicity.

The sources of the data presented in the graphs are: Redfors, Br Heart J 1972;34:383-91 for change in ventricular rate v plasma digoxin concentration; Smith, Huber, J Clin Invest 1970;45:2377-86 for plasma digoxin concentrations in toxic and non-toxic patients; Lloyd et al, Am J Cardiol 1978;42:129-36 for plasma digoxin concentration v time; and J K Aronson, PhD thesis for digoxin reaching steady state. The data are reproduced with permission of the journals.

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