

Management of digoxin toxicity

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SUMMARY

Digoxin toxicity can emerge during long-term therapy as well as after an overdose. It can occur even when the serum digoxin concentration is within the therapeutic range.

Toxicity causes anorexia, nausea, vomiting and neurological symptoms. It can also trigger fatal arrhythmias. There is a range of indications for using digoxin-specific antibody fragments. The amount ingested and serum digoxin concentration help to determine the dose required, but are not essential.

Digoxin-specific antibody fragments are safe and effective in severe toxicity. Monitoring should continue after treatment because of the small risk of rebound toxicity.

Restarting therapy should take into account the indication for digoxin and any reasons why the concentration became toxic.

Introduction

Digoxin can be used to treat heart failure when symptoms remain despite the use of other drugs. It is also used for atrial fibrillation to reduce the ventricular rate.¹ For heart failure, the recommended range for the serum digoxin concentration has been reduced over the past decade from 0.8–2.0 nanogram/mL to 0.5–0.9 nanogram/mL.² This is because of evidence of better outcomes at lower concentrations.³ Whether this range should also apply to patients with atrial fibrillation without heart failure is unknown.

Incidence of toxicity

Digoxin use has declined since the 1990s.⁴ While the overall incidence of toxicity per population has also declined, the incidence per treated patient may have remained unchanged.^{4,5} The Australian Institute of Health and Welfare records cardiac glycoside toxicity as the diagnosis on hospital discharge in 280, 233 and 139 patients in 1993–94, 2003–04 and 2011–12 respectively.⁶ Chronic toxicity is far more common than acute intoxication.⁷

Digoxin pharmacology

Digoxin increases intracellular calcium in myocardial cells indirectly, by inhibiting the sodium–potassium pump in the cell membrane. Increased intracellular calcium increases cardiac contractility, but also the risk of tachyarrhythmias.⁸ Inhibition of this pump causes the hyperkalaemia commonly seen in toxicity. Digoxin also causes an increase in vagal activity, reducing activity in the sinus node and prolonging conduction in the atrioventricular node.

After a dose of digoxin, distribution to the tissues takes several hours. This means that the serum

digoxin concentration is inaccurate unless taken at least six hours after the last dose. Only a post-distribution measurement reflects the severity of intoxication and this is the measurement that can help when calculating the dose of digoxin-specific antibody.⁹ This applies in both acute and chronic poisoning.

The elimination of digoxin is mainly by renal clearance and is prolonged in patients with renal impairment. Transport by P-glycoprotein also contributes to elimination.⁸ Consequently, a higher serum digoxin concentration for a given dose occurs in patients with renal impairment, lower body weight and in those taking amiodarone, verapamil, macrolides, azole antifungals and cyclosporin, which inhibit P-glycoprotein transport.¹⁰

Although the serum digoxin concentration does predict the likelihood of toxicity,^{8,11} several conditions increase sensitivity to digoxin. They at least partly account for patients who develop toxicity when their serum digoxin concentration is within the therapeutic range.¹¹ These conditions include hypokalaemia, hypomagnesaemia, hypercalcaemia, myocardial ischaemia, hypoxaemia and acid–base disturbances.¹⁰

Clinical features

The clinical features of toxicity are often non-specific. They commonly include lethargy, confusion and gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhoea and abdominal pain).¹⁰ Visual effects (blurred vision, colour disturbances, haloes and scotomas) are rarer in contemporary practice.⁸ Cardiac arrhythmias account for most deaths.⁹

Arrhythmias can occur even if the patient has no symptoms. Almost any arrhythmia can occur, with the exception of atrial tachyarrhythmias with a rapid ventricular response,⁸ because these usually require intact conduction in the atrioventricular node. Characteristic arrhythmias are those in which a tachyarrhythmia occurs simultaneously with sinus or atrioventricular node suppression, such as atrial and junctional tachycardia with atrioventricular block. However, sinus bradycardia, atrioventricular block and ventricular ectopy are more common.¹² With severe toxicity, ventricular tachycardia (which may be bidirectional) and ventricular fibrillation can occur. 'Reverse tick' T-wave inversion is not a sign of toxicity.

Treatment

There are no evidence-based guidelines for the management of mild to moderate toxicity so there is a wide variation in treatment.¹³ Severe toxicity requires hospital admission and consideration of the need for digoxin-specific antibody fragments. Although digoxin-specific antibody fragments are safe and effective, randomised trials have not been performed.

The antibody fragments form complexes with the digoxin molecules. These complexes are then excreted in the urine.

Indications for digoxin-specific antibody fragments

The indications for digoxin-specific antibody fragments are inconsistent. Four contemporary sources^{1,9,14,15} recommend administration for strongly suspected or known digoxin toxicity with:

- life-threatening arrhythmia
- cardiac arrest
- potassium >5.0 mmol/L (significant hyperkalaemia is a strong indication for treatment because of its association with a poor prognosis if digoxin-specific antibody fragments are not given¹⁶).

However, the same sources vary in their recommendations for administration when there is:

- acute ingestion of >10 mg in adults or >4 mg in children
- evidence of end-organ dysfunction
- moderate to severe gastrointestinal symptoms
- serum digoxin concentration >12 nanogram/mL
- significant clinical features of digoxin toxicity with serum digoxin concentration >1.6 nanogram/mL.

Such disagreements over when to use digoxin-specific antibody fragments arise from cost-benefit, not harm-benefit, considerations. The cost is roughly \$1000 per ampoule and several ampoules may be

used. However, economic arguments have been made for their use in non-life-threatening toxicity, as the duration of hospitalisation may be reduced.¹⁷

Dose and administration

Only one formulation is available in Australia. Each ampoule contains 40 mg of powdered digoxin-specific antibody and is reconstituted with 4 mL of water. This can be given as a slow push in cardiac arrest, but otherwise the total dose is diluted further with normal saline and infused over 30 minutes.

The response begins about 20 minutes (range 0–60 min) after administration. A complete response occurs in 90 minutes (range 30–360 min).¹⁴

Conventional dosing protocols aim to neutralise total body digoxin completely. The total dose is usually expressed in vials. It depends on whether the post-distribution serum digoxin concentration is known, the amount ingested is known, or neither is known.¹⁵

Known digoxin concentration

If the post-distribution concentration is known (in either acute or chronic ingestion), knowing the amount ingested is unnecessary. The dose is:

number of vials = post-distribution serum digoxin concentration (nanogram/mL) x weight (kg)/100 (multiply by 0.78 if SI units are used for post-distribution serum digoxin concentration).

Known amount ingested

If the quantity of digoxin ingested is known, but the post-distribution serum digoxin concentration is unknown, the dose is:

number of vials = amount ingested (mg) x 2 x 0.7 (0.7 is the bioavailability of digoxin tablets supplied in Australia).

Unknown data

When neither the post-distribution serum digoxin concentration nor the amount ingested is known, use empiric dosing. Repeat in 30 minutes if the response is inadequate. The dose is:

for adults and children greater than 20 kg

- five vials if haemodynamically stable
- 10 vials if unstable

for children less than 20 kg

- one vial.

Other regimens

Some authors have argued for modification of the calculated doses to be given as an initial half dose followed by either further doses as required¹⁸ or an infusion.¹⁹ These suggestions follow from the view that full dosing is unnecessary to achieve tolerable

concentrations of digoxin and may be undesirable in patients who need digoxin.^{18,20} There are also concerns that significant amounts of digoxin-specific antibody fragments may be eliminated before full removal of digoxin from tissue stores.¹⁹ Furthermore, in practice many hospitals will not stock sufficient ampoules for the full calculated dose. In this case specialist toxicological advice should be sought on the adequacy of modified dosing.

Precautions and adverse effects

Hypomagnesaemia and, more importantly, hypokalaemia (common with diuretic use) should be corrected before or during administration because digoxin-specific antibody fragments will further lower potassium.¹⁴ Hypokalaemia occurs as a result of treatment in about 4% of patients.²¹ Serum potassium should be frequently monitored.¹⁴

'Rebound' toxicity¹⁴ is the reappearance of toxicity after an initial response to digoxin-specific antibody fragments. This occurs in about 2% of patients given a full neutralising dose.²¹ It can develop 12–24 hours after treatment, but up to 10 days later in patients with renal failure.¹⁴ Serum digoxin concentration is of no use in diagnosis, because it measures the digoxin in the complexes with antibody fragments as well as unbound digoxin. The concentration therefore rises many fold after digoxin-specific antibody fragments are given even in the absence of rebound toxicity.²²

Heart failure or atrial fibrillation with rapid ventricular response (presumed re-emergent due to removal of digoxin effect) occurs in up to 3% of patients.¹⁴ Allergic reactions occur in about 1% of infusions.²¹

Other treatments

Other treatments for severe toxicity should be seen as temporising or adjunct measures, rather than alternatives to digoxin-specific antibody fragments. Activated charcoal²³ can be used in patients who present within two hours of acute ingestion.

Hyperkalaemia will improve with giving digoxin-specific antibody fragments, and conventional treatments such as calcium will generally be unnecessary or harmful.¹⁵ If the patient has severe hypokalaemia and digoxin toxicity, it is important to correct the serum potassium.

Lignocaine⁸ can be used for ventricular tachyarrhythmias and atropine¹⁵ for bradyarrhythmias. Cardioversion, which can result in ventricular fibrillation, should be avoided.

In cardiac arrest, resuscitation efforts should be continued for at least 30 minutes after giving digoxin-specific antibody fragments.

Restarting digoxin

When considering restarting digoxin, first determine whether the patient's indication for use and target serum digoxin concentration were consistent with current guidelines, as these have changed markedly over the past couple of decades. Digoxin can be resumed after adjusting the dose for changes in target serum digoxin concentration, renal function and weight if necessary. This should be delayed until all the digoxin-specific antibody fragments have been cleared, which will take up to a week, but far longer in the presence of renal dysfunction.^{18,22}

Conclusion

Digoxin toxicity has declined, possibly as a result of a decreasing use and a reduced recommended therapeutic range. It can occur when serum digoxin concentration is within the therapeutic range and, as the presenting features are usually non-specific, the diagnosis can be difficult.

Digoxin-specific antibody fragments are used when there is a risk of a life-threatening arrhythmia. The decision to use digoxin-specific antibody fragments is not dependent on knowledge of the serum digoxin concentration or the amount of digoxin ingested, but when either of these is known they should be used to calculate the dose. Further research is needed into optimal dosing protocols and whether digoxin-specific antibody fragments can be cost-effectively used for non-life-threatening toxicity. ◀

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SELF-TEST QUESTIONS

True or false?

5. Digoxin toxicity can occur when the serum digoxin concentration is within the reference range.

6. Concentrations of serum digoxin should be measured within six hours of a dose.

Answers on page 27

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