Module 5.4
Digoxin

Introduction

Cardiac glycosides, like digoxin, are prescribed in the management of chronic atrial fibrillation, particularly in the setting of cardiac failure. They inhibit the Na^+/K^+ ATPase pump, leading to intracellular accumulation of Ca^{2+} and improved cardiac automaticity and contractility. Ingestion of naturally occurring cardiac glycosides like oleander and cane toad venom can also lead to poisoning.

A digoxin-Fab fragment is available to bind circulating digoxin and counteract toxicity. It is indicated in the setting of significant arrhythmia and can reduce morbidity, mortality and length of stay.

Toxicokinetics[1]

Digoxin is water soluble with a bioavailability between 60 and 80%. Its average plasma half-life is 40h, but can be prolonged to more than 100h in renal failure. It has a large volume of distribution of 5–10 L/kg with extensive tissue distribution and low protein binding (20%). It is predominantly excreted by the kidneys.

Oleander and cane toad venom undergo extensive enterohepatic circulation[1] making them amenable to MDAC decontamination.

Risk Assessment

Digoxin poisoning results in nausea, vomiting and diarrhoea. More importantly it causes cardiac conduction abnormalities. Bradyarrhythmias (AV nodal block, slow AF), accelerated escape rhythms and ventricular tachycardias can all occur.

Digoxin toxicity can be either **acute**, usually following an intentional overdose, or **accumulation**, often occurring when patients on long term digoxin therapy have a deterioration in the renal function. Whilst the provision of digoxin-Fab in acute toxicity can be life-saving, its role in digoxin accumulation is limited[2].

Hypokalemia, hypomagnesemia, hypercalcemia, hypoxia, ischemic heart disease, hypothyroidism and advanced age all increase the likelihood of chronic digoxin accumulation[3].

All patients require an urgent ECG, digoxin level and electrolytes (including magnesium). These will need to be performed serially to track progress. Once Digoxin-Fab has been given the digoxin level cannot differentiate between free and bound digoxin so is not useful clinically. Free digoxin assays are available at some centres.

Management

Resuscitation

Acute toxicity

Life threatening arrhythmia is an indication for Digoxin-Fab therapy. Hypokalaemia and hypomagnesaemia should be corrected. Atropine can be given for significant bradycardia, initially, while sourcing Digoxin-Fab fragment.

Chronic accumulation

Whilst Digoxin-fab can be given in the setting of ventricular arrhythmia or bradycardia leading to hypotension, this is not common. Patients with chronic accumulation commonly present with bradycardia, without haemodynamic compromise. In these patients, management should focus on correction of hyperkalaemia and withholding nephrotoxins and other rate limiting medications, such as β-blockers and CCB.

Decontamination

SDAC should be administered in the co-operative patient following an acute digoxin overdose of >0.1mg/kg who presents within 2 hours[4], or at any stage following oleander or cane toad venom poisoning.
MDAC should be administered in oleander or toad venom poisonings[5].

Antidote

Digoxin-Fab fragment should be administered if there is an **arrhythmia associated with haemodynamic instability or evidence of automaticity**.
While equations exist to calculate the body load of digoxin and subsequent dose of Fab fragment required this overestimates the total amount required due to the toxicokinetics (specifically the distribution) of digoxin.

A far more practical approach is[1]

Acute toxicity:	**give 2 vials & repeat hourly as required**
Chronic toxicity:	**give 1 vial & repeat hourly as required**

Recent research[5] has highlighted the limited role of digoxin-Fab in patients with chronic accumulation as it produced a median increase in heart rate of 8 beats per minute in a group of 36 patients. This group typically has multiple co-morbidities and take multiple cardiovascular medications such as beta blockers, calcium channel blockers and ACE inhibitors. Digoxin-Fab should not be relied upon in isolation to improve heart rate nor correct hyperkalaemia in patients with chronic accumulation, this is in contrast to acute poisoning where it is the first line agent in severe toxicity.

Supportive Measures

Patients should be observed on telemetry in the Short Stay Unit. Antiemetics should be prescribed to limit vomiting and any associated vagal surge. Maintain normal ranges for potassium and magnesium.

Disposition

Given the potential for cardiotoxicity, all patients with acute digoxin poisoning should be discussed with the toxicology team. A prolonged period of observation is required following Fab fragment administration to ensure that there is no rebound toxicity once tissue redistribution has occurred.

Further reading

- Chan B and Buckley N. "Digoxin-specific antibody fragments in the treatment of digoxin toxicity." *Clin Toxicol* 2014; DOI: 10.3109/15563650.2014.943907
- Chan B, Isbister G, O'Leary M, Chiew A & Buckley N. Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1), *Clin Toxicol*. 2016; DOI: 10.1080/15563650.2016.1175620

References

1. Chan B and Buckley N. "Digoxin-specific antibody fragments in the treatment of digoxin toxicity." *Clin Toxicol* 2014; DOI: 10.3109/15563650.2014.943907
2. Chan, B.S., et al., Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4). Clin Toxicol (Phila), 2018: p. 1-6.
3. Abad-Santos F, Carcas A, Ibanez C and Frias J. "Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity." *Therapeutic Drug Monitoring* 2000;22(2):163-8
4. Wikitox Digoxin 2.1.6.1.2 http://www.wikitox.org/doku.php?id=wikitox:2.1.6.1.2_cardiac_glycosides
5. Eddleston M et al. "Anti-digoxin Fab fragment in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial." *Lancet* 2000; 355:967-72
6. Chan B, Isbister G, O'Leary M, Chiew A & Buckley N. Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-

1), *Clin Toxicol*. 2016; DOI: 10.1080/15563650.2016.1175620