Chronic Digoxin Toxicity: Does it even exist??

GEMSEM 2018
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Mrs PC, an 85yo F (78kg) presents after a fall;

- PMSH of IHD, CCF, AF and COPD
- Meds digoxin, amiodarone, metoprolol, spironolactone, frusemide & aspirin
- O/E looks dry, HR 30, BP 180/70
- K⁺ 5.8, creat 190, digoxin 3.8 (0.8-2.0)
Management thoughts?

DigiFab?

Treat hyperkalaemia? Calcium?

Other management?
Correct hypokalemia and hypomagnesemia; do not give calcium. Digoxin-specific antibody fragments (Fab) indicated if patient has hemodynamically significant arrhythmias, serum potassium $\geq 5$ mEq/L if acute overdose, Mobitz II or third-degree AV block, ingestion of bufadienolide- or cardenolide-containing agents, or renal insufficiency.
What the textbooks say...

Empirical dose
Chronic: 2-5 vials
Acute: 10-20 vials

Calculated dose
Chronic: number of vials = $2 \times$ serum digoxin level (ng/mL) $\times 5.6 \times$ weight (kg)/1000
Acute: number of vials = $2 \times$ oral digoxin dose (mg) $\times 0.8$

For this patient 3.3 vials
What the evidence says...

**Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1)**

Betty S. Chan, Geoffrey K. Isbister, Margaret O’Leary, Angela Chiew and Nicholas A. Buckley

ABSTRACT

**Context:** We hypothesized that in chronic digoxin toxicity, anti-digoxin antibodies (Fab) would be efficacious in binding digoxin, but this may not translate into improved clinical outcomes. **Objective:** This study aims to investigate changes in free digoxin concentrations and clinical effects on heart rate and potassium concentrations in chronic digoxin poisoning when anti-digoxin Fab are given. **Materials and methods:** This is a prospective observational study. Patients were recruited if they have been treated with anti-digoxin Fab for chronic digoxin poisoning. Data was entered into a standardised prospective form, supplemented with medical records. Their serum or plasma was collected, analysed for free and bound digoxin and free anti-digoxin Fab concentrations. **Results:** From September 2013 to February 2015, 36 patients (median age, 78 years; 22 females) were recruited from 18 hospitals. Median heart rate (HR) was 49 beats/min. Initial median digoxin and potassium concentrations were 4.7 nmol/L (3.6 µg/L) (range: 2.3–11.2 nmol/L) and 5.3 mmol/L (range: 2.9–9.2 mmol/L) respectively. Beta-blockers...
Setting

Australian study: DORA arm ATOM

Inclusion criteria

– Digoxin > 2.6 μg/L
– Symptoms toxicity
  • Arrhythmia
  • Hyperkalaemia
  • Renal failure
– Given digifab
Methods

• Prospective observational study

• Investigate clinical syndrome of chronic digoxin poisoning
  – Measure levels (digoxin, digiFab & free digoxin)
  – Response to digiFab with ΔHR and Δ[K+]
## Results

<table>
<thead>
<tr>
<th>Table 1: Patient demographics and baseline characteristics.</th>
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<tbody>
<tr>
<td><strong>Total number of patients</strong></td>
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<tr>
<td><strong>Median age</strong></td>
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<tr>
<td><strong>Female (%)</strong></td>
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<tr>
<td><strong>Body weight (kg)</strong></td>
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<td><strong>Median daily digoxin dose (µg)</strong></td>
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<td><strong>Median creatinine concentration</strong></td>
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<td><strong>Median initial potassium concentration</strong></td>
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<td><strong>Median heart rate (min⁻¹)</strong></td>
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<td><strong>HR ≤45 (min⁻¹)</strong></td>
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<tr>
<td><strong>Median initial systolic blood pressure (mm Hg)</strong></td>
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<tr>
<td><strong>Median initial total digoxin concentration</strong></td>
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<tr>
<td><strong>Median no. vials anti-digoxin Fab used</strong></td>
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<tr>
<td><strong>No. patients taking beta-blockers (%)</strong></td>
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<td><strong>No. patients taking calcium antagonists (%)</strong></td>
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<tr>
<td><strong>No. patients taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers and/or spironolactone (%)</strong></td>
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IQR: interquartile range.
**Figure 1.** Scatter plot of the pre-treatment digoxin concentration (nmol/L) for each dosing group of anti-digoxin Fab with median and 25 and 75 percentile indicated: one vial (40 mg; 10 patients), two vials (80 mg; 16 patients), and three or more vials (120–400 mg; 10 patients). Conc: concentration.
• Median Δ HR after digiFab was 8 bpm
• Median $\Delta K^+$ after digiFab was 0.3 mmol/L.
Drug levels

- Free digoxin fell to almost zero regardless of dose used
- Free digiFab levels detectable in all patients
- Rebound in 25 patients
  - 9 rebounded > 1.5μmol/L
  - Median peak at 15h
  - No further digiFab required
What the evidence says...

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REVIEW ARTICLE

**Digoxin-specific antibody fragments in the treatment of digoxin toxicity**

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**Context.** Digoxin-specific antibody fragments (digoxin-Fab) are widely regarded as a safe and effective treatment for the management of acute and chronic digoxin poisoning. Calculated equimolar doses of digoxin-Fab are high, very expensive, and infrequently used. **Objective.** To review the pharmacology, efficacy, effectiveness, indications, safety and the dosage of digoxin-specific antibody fragments. **Methods.** Pubmed, Embase, Medline and Cochrane were searched from 1946 to May 2013 using the terms digoxin, digoxin-specific Fab, and digoxin antibody. **Pharmacology and kinetics of digoxin and digoxin-Fab.** Digoxin acts via inhibition of Na⁺/K⁺ ATPase. It has a narrow therapeutic index. Digoxin has 60–80% bioavailability, a mean plasma half-life of 40 h and a volume of distribution (Vd) of 5–10 L/kg and low protein binding (20%). A 40-mg vial of digoxin-Fab (DigiFab) binds 0.5 mg digoxin. Digoxin-Fab has a mean plasma half-life of 19–30 h and a Vd of 0.4 L/kg. The half-lives of both digoxin and digoxin-Fab are prolonged in renal failure to over 100 h. **Efficacy and effectiveness of digoxin-Fab.** There were no randomised clinical trials examining the use of digoxin-Fab for acute or chronic digoxin poisonings. Ten case series with a total of 2,080 patients have reported on the use of digoxin-Fab in digoxin poisoning. In three large case series of 430 acute and 1280 chronic poisonings digoxin-Fab was more effective than digoxin alone in reducing digoxin concentration.
Assumptions were wrong

Digoxin very large Vd of 5-10L/kg
• distributed & re-distributed

2 compartment model:

• Central compartment $\mu g/L \times 55L$
• Peripheral compartment $\mu g/L \times 330L$
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- O/E looks dry, HR 30, BP 180/70
- K⁺ 5.8, creat 190, digoxin 3.8 (0.8-2.0)

3.8μg/L x 55L = 209μg circulating digoxin

One vial of digiFab binds 0.5mg digoxin

Dose is 0.4 vial
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If you called me at Poison’s.....
Summary

1. Digoxin is rarely the sole culprit

2. “Chronic Digoxin Toxicity” is rare

3. Reserve DigiFab for
   – Haemodynamic instability
   – Automaticity

4. If you give DigiFab 1 – 2 vials is plenty