Case 028: A case of seeing yellow.

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A 76 year old woman came to the Clinic complaining of anorexia, nausea, vomiting, headache, dizziness, and blurring of vision. Five days ago she went to see a private doctor who gave her some medications for fever, runny nose, and cough. Although she has recovered from her fever, the symptoms of upper respiratory tract infection gave way to the new complaints mentioned above.

On further questioning, the patient claimed her visual complaint was in the form of yellow green visual distortion. Concurrent illnesses included atrial fibrillation, hypertension, and dilated cardiomyopathy treated with aspirin, digoxin, frusemide, hydralazine, and isosorbide since 3 years ago. Warfarin was not prescribed for thromboembolic prophylaxis because of an alleged allergy. When asked about the medications prescribed for her common cold, she produced a bag containing a bottle of syrup and some capsules that were impossible to identify.

Physical examination revealed a female of stated age. Her oral temperature was 37.2 °C, respiratory rate 20/min, and BP 140/80 mmHg. Her pulse was irregularly irregular and the rate was 52 when counted over 1 minute. She was not in respiratory distress and not cyanotic; her jugular venous pressure (JVP) was elevated; there were fine basal crepitation in her chest bilaterally and mild pitting edema at her ankles; her abdomen was unremarkable. She was somewhat confused with time and place and had difficulty following complex instructions but there were no focal neurological deficits. Visual acuity was corrected to normal by her eye glasses; visual field by confrontation and eye movements were normal; pupils were equal and reacted to light directly and consensually.

1. What are the differential diagnoses?

This patient has symptoms and signs that can be related to 3 systems:
The gastroenterological system: anorexia, nausea, vomiting.
The central nervous system: headache, dizziness, blurring of vision, disorientation, and difficulty following complex instructions.
Cardiovascular system: slow atrial fibrillation, elevated JVP, basal crepitation, and pitting edema.

When taken in isolation, these symptoms and signs suggest separate disturbances in these systems, including gastroenteritis, dementia, latent cerebral hemorrhage, sepsis, heart failure due to progress of underlying disease or improper treatment. But when the symptoms and signs of all 3 systems are taken together, digoxin toxicity is a likely possibility.

2. What is digoxin and what are its pharmacological actions?

Digoxin is the most popular member of a family of drugs called the cardiac glycosides. Although it has side effects on other systems, its utility lies in the treatment of cardiovascular disease:
- To control the ventricular rate in atrial fibrillation because of its ability to slow AV conduction.
- To treat mild to moderate heart failure because of its ability to increase the force of myocardial contraction.

It achieves these actions through 2 separate mechanisms and toxicity is an exaggeration of these actions:
- It is a vagomimetic agent capable of slowing sinus node discharge and AV node conduction. At toxic levels, it can cause sinus arrest and heart block. These vagal effects can be reversed with the administration of atropine.
- It binds the adenosine triphosphatase (ATPase) of and paralyzes the Na⁺-K⁺ pump of myocardial cell membranes, which is responsible for exchanging intracellular Na⁺ for extracellular K⁺. With this pump inactivated, the pump responsible for the exchange of Na⁺ for Ca²⁺ is stimulated. The net result is an increase in sarcoplasmic Ca²⁺ and a decrease in intracellular K⁺. The increased availability of Ca²⁺ in the sarcoplasmic pool during excitation-contraction coupling of myocardial fibers is responsible for the therapeutic effect of improved myocardial contractility. At toxic levels, however,
intracellular Ca\(^{2+}\) excess and K\(^+\) deficit will lead to enhance automaticity and excitability of secondary pacemaker tissues, resulting in increased ectopic activities.

Digoxin is readily absorbed through the gastrointestinal tract with a bioavailability of 80%. Skeletal muscle is a major compartment in its volume of distribution. With decreased muscle bulk, geriatric patients are more sensitive to this drug than younger patients. It is dependent on the kidneys for elimination and clearance is reduced in patients with renal dysfunction. The therapeutic plasma level is 0.6 – 2.6 ng/ml but there is considerable overlap between therapeutic and toxic concentrations.

3. What are the clinical manifestations of digoxin toxicity?

The symptoms and signs of digoxin toxicity are non-specific. In general, the following complaints in a patient on digoxin or other cardiac glycosides should raise suspicion:

**General**
- Malaise, weakness, dizziness.

**Gastrointestinal**
- Anorexia, nausea and vomiting, diarrhea, abdominal discomfort that can be vague and nonspecific.

**Ophthalmic**
- Blurring of vision, photophobia, light flashes, scotoma, halo around objects, objects appearing yellow.

**Neuro-psychiatric**
- Parasthesia, headache, vertigo, memory loss, disorientation, confusion, delirium, hallucination, dementia, seizures, psychosis.
Cardiovascular
- Digoxin intoxication can precipitate any and all types of arrhythmia and no particular type is pathognomonic. The common ones include sinus bradycardia, ventricular premature beats, heart blocks, and atrial fibrillation with a high degree of AV block and slow ventricular response as in this patient. More than one type of arrhythmia can coexist in the same patient.
- Precipitation of congestive heart failure or worsening of existing heart failure is a common and deceptive complication of digoxin toxicity.

4. What investigations are indicated in this patient?

Essential investigation in this patient should include:
- Complete blood counts. Occult anemia and infection are common precipitating causes of congestive heart failure.
- Plasma digoxin level. Toxicity is related to high plasma level although intoxication still can occur when plasma level is in the therapeutic range due to presence of factors that enhance toxicity.
- Plasma electrolyte levels including that of potassium and magnesium. Hypokalemia and hypomagnesemia from chronic diuretic use can potentiate the toxic effect of digoxin and other cardiac glycosides.
- Renal function tests. Digoxin is eliminated primarily by renal excretion and deterioration in renal function can be a cause of digoxin toxicity after a period of stable therapy.
- ECG to determine the nature of the arrhythmia.
- Chest x-ray because of the clinical signs of heart failure.
- Unknown drugs to pharmacy for identification.

Other less urgent tests that can help to shed light on this patient’s mental state include dementia screening with thyroid function tests, plasma vitamin B₁₂ and folate levels, screen for syphilis infection by VDRL, and CT scan of brain.
Patient’s progress in hospital – The results of laboratory investigations were:

<table>
<thead>
<tr>
<th>Blood</th>
<th>Reference range</th>
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<tbody>
<tr>
<td>RBC</td>
<td>4.20 – 5.70 10^{12}/L</td>
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<tr>
<td>Hgb</td>
<td>13.2 – 16.7 g/dL</td>
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<tr>
<td>HCT</td>
<td>0.39 – 0.5 L/L</td>
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<tr>
<td>MCV</td>
<td>81.0 – 97.0 fL</td>
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<tr>
<td>MCH</td>
<td>27.0 – 32.0 pg</td>
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<tr>
<td>MCHC</td>
<td>31.0 – 35.0 g/dL</td>
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<tr>
<td>Platelet</td>
<td>140 – 380 10^9/L</td>
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<tr>
<td>WBC</td>
<td>4.0 – 10.8 10^9/L</td>
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<table>
<thead>
<tr>
<th>Plasma</th>
<th>Therapeutic range</th>
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<tbody>
<tr>
<td>Digoxin</td>
<td>0.6 – 2.6 ng/ml</td>
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<thead>
<tr>
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<tr>
<td>Na^+ 128* 134 – 145 mmol/L</td>
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<tr>
<td>K^+ 3.0* 3.5 – 5.1 mmol/L</td>
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<tr>
<td>Urea 7.4 3.4 – 8.9 mmol/L</td>
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<tr>
<td>Creatinine 125* 62 – 106 µmol/L</td>
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<tr>
<td>Magnesium 0.7 0.67 – 1.01 mmol/L</td>
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12-lead ECG showed atrial fibrillation with a heart rate of 48/min. Chest x-ray (erect PA film) showed a cardiothoracic ratio of 0.51 with redistribution of blood flow to the upper zones but no signs of consolidation. Pharmacy reported that the syrup was a common cough medicine containing guaifenesin (a harmless expectorant) and the capsules were clarithromycin.

5. What can be said of these findings?

Hyponatremia in this patient is consistent with increased sodium loss from chronic diuretic therapy and is of no clinical significance because of its mild magnitude. The mildly elevated creatinine is most likely the result of renal
dysfunction associated heart failure and would correct itself once cardiac function is returned to normal. The most significant findings are the elevated digoxin level above therapeutic range, the hypokalemia, and concurrent medication with clarithromycin.

6. What is the explanation for the elevated plasma digoxin level and development of toxicity after years of stable therapy in this patient?

There are 3 important factors contributing to the development of digoxin toxicity in this patient:

- This patient’s concurrent medication with the macrolide antibiotic clarithromycin is the most important cause of elevated plasma digoxin concentration. Two concurrent mechanisms are at play in this drug-drug interaction:
  - Clarithromycin inhibits the P-glycoprotein mediated renal tubular secretion of digoxin.
  - Part of ingested digoxin is broken down by enteric bacteria in some patients. Antibiotics (clarithromycin, erythromycin, tetracycline), by altering the bacterial flora in the gastrointestinal tract, can decrease the magnitude of this breakdown and increase the bioavailability of digoxin.

Other drugs that have been reported to increase plasma digoxin level include: amiodarone, verapamil, nifedipine, diltiazem, quinidine, propafenone, carvedilol, spironolactone, amiloride, triamterene, indomethacin, alprazolam, itraconazole, cyclosporine, and the herbal medicine St. John’s wort.

- Renal dysfunction in this patient also contributes to decreased digoxin renal clearance and increased plasma concentration.

- Hypokalemia seen in this patient enhances digoxin toxicity. This is because extracellular potassium competes with digoxin for binding to Na⁺-K⁺-ATPase. When plasma K⁺ is low, digoxin is left to bind more avidly to the pump and inhibit its action.
7. What is the guiding principle in the management of digoxin toxicity?

The following principle of treatment applies to all cardiac glycoside toxicity, not just digoxin.

General measures
- Admit the patient to an area where vital signs, oxygen saturation, and ECG can be monitored continuously.
- Give oxygen supplement as indicated.
- Treat hypotension.
- Maintain acid-base balance normal.
- Maintain fluid balance, taking into account that worsening of heart failure is a complication of toxicity.

Strategies to reduce plasma digoxin level
- Discontinue the administration of digoxin. In case of atrial fibrillation with a fast ventricular response, another class of rate controlling drugs may have to be prescribed (β antagonists, calcium channel antagonists, amiodarone).
- Stop clarithromycin and switch to another antibiotic that does not interact with digoxin if anti-microbial therapy is still indicated.
- Improve renal function. (Digoxin is not removed effectively by hemodialysis.)

Remove factors than can enhance toxicity
- Correct hypokalemia if present. It is worthwhile to maintain plasma potassium at the upper limit of normal to suppress the binding of digoxin to Na⁺-K⁺-ATPase.
- Correct hypomagnesemia if present. Hypokalemia and hypomagnesemia are common complications of chronic diuretic therapy. Aside from replenishing deficits, magnesium administration can also antagonize toxic digoxin effects directly.
Treat arrhythmias

- Treat bradyarrhythmias and heart blocks with atropine. Isoproterenol is also effective but has the propensity to increase ventricular ectopy. Cardiac pacing may be indicated when bradyarrhythmias are refractory to drug treatment. But bear in mind that pacing threshold is increased (making it more difficult to pace) and fibrillation threshold is decreased (making it easier to precipitate ventricular fibrillation) in cases of toxicity.
- Treat ventricular irritability with phenytoin or lidocaine. Both drugs can suppress ventricular automaticity without significantly slowing AV conduction. Quinidine and procainamide are contraindicated because they slow AV conduction.
- Life-threatening tachyarrhythmias may require cardioversion. But this procedure should be dispensed only as a last resort starting with very low energy settings because it can precipitate bizarre ventricular arrhythmias and fibrillation.

8. What is Fab and when should it be used?

Digoxin specific antibody fragments (Fab) produced by cleavage of sheep immunoglobulin antibodies to digoxin are marketed as Digibind. These antibody fragments are capable of binding and inactivating digoxin. Onset of action ranges from 20 – 90 minutes and a complete response generally occurs within 4 hours. It has also been used successfully to treat digitoxin overdose. Where available Fab is considered to be the first line drug in the following life-threatening situations:
- Severe ventricular arrhythmias such as ventricular tachycardia or fibrillation.
- Progressive bradyarrhythmias such as severe sinus bradycardia or second or third degree heart block not responding to atropine.
- Acute digoxin overdose in which:
  - Healthy children have swallowed > 4 mg or healthy adult have ingested > 10 mg of digoxin; or
  - The steady-state plasma concentration 6 – 8 hours following ingestion is 10 ng/ml or more; or
- Plasma K+ increases progressively to 5 mmol/L or more following digoxin ingestion.

The manufacturer of Digibind does not recommend Fab to be used in milder cases of toxicity.

Further readings


