CV Podcast 8 Digitalis

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Learning Objectives: Upon completion of this activity, participants will be able to…

- Review the pharmacology of digitalis glycosides, specifically digoxin
- Discuss the mechanism of action of digoxin and its primary uses in anesthesia and critical care medicine
- List the features of acute and chronic digitalis/digoxin toxicity

Hello, my name is Max Ofoma. I am a medical student at the Indiana University School of Medicine and I am joining Dr. Timothy Webb who is a clinical assistant professor of anesthesia at the Indiana University School of Medicine. Today we'll be covering the drugs digitalis and digoxin.

Let's start with some history. In the 18th century, digitalis was discovered. It is a cardio-active drug derived from the leaves of the poisonous flower, *Digitalis purpurea*. The name "Digitalis" is from the Latin *digitus*, or finger, referencing its long, pendulous, bell-shaped characteristics. The flower is native to Europe and more commonly called the Common Foxglove. Well-known since the Dark Ages, the Common Foxglove digitalis extract has been utilized for various purposes – as a "healing herb," to treat boils and ulcers, to use as a poison, to test the innocence or guilt of the accused during the medieval Trial by Ordeal. In folklore, it was said that picking a foxglove would offend fairies, a tale told to children to protect them from the fatally toxic nature of the plant. It's fascinating to ponder how the extract from such a deadly plant became a cardiotonic agent in contemporary medicine. We are here to help you understand why digitalis carries this potential.

Now that we've discussed the background of this drug, let's talk about the pharmacodynamics. As you recall pharmacodynamics is the study of the biochemical, physiologic and molecular effects a drug has on the body. More easily put, pharmacodynamics describes what the drug does to the body. In order to have a better understanding of how digitalis is utilized, we will discuss its more common preparation, digoxin.

Digoxin belongs to a group of medications known as cardiac glycosides. The medication's overall effect results in increased inotropy (or increased squeeze) and a reduction in chronotropy (or a reduction in heart rate). Digoxin's mechanism of action includes inhibition of the sodium potassium adenosine triphosphatase (also known as sodium potassium ATPase) enzyme in the sarcolemma. This results in an increase in intracellular sodium, which then subsequently promotes an increase in the intracellular calcium concentration through the sodium-calcium exchanger. In addition, the increase in intracellular

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calcium concentration promotes the intracellular influx of calcium through the slow calcium channels. The additional calcium available to the contractile proteins results in increased contractility and thus increased inotropy. Furthermore, the increase in intracellular calcium also lengthens the refractory period of the cardiac conducting tissue, resulting in a reduction in heart rate. Digoxin also has direct and indirect effects on the parasympathetic system (including via the vagus nerve) which slows conduction through the AV node which also contributes to the reduction in chronotropy.

Now that we have a better understanding of how this medication works, how can the inotropic and chronotropic effects of digoxin be applied to patients in a clinical setting? We'll briefly examine the basic pathogenesis of atrial fibrillation and heart failure to understand when this medication is clinically appropriate for use.

The pathogenesis of atrial fibrillation or "a-fib" most commonly involves "initiating triggers." This comes in the form of rapidly firing ectopic foci located anywhere besides the SA node. Abnormal atrial tissue due to structural valve disease or ischemia, for example, is then capable of maintaining the arrhythmia. In afib, both the increase in heart rate (with less filing time) and loss of normal sinus rhythm resulting in loss of atrial kick, can ultimately result in hemodynamic instability. This instability is seen as reduction in blood pressure, and eventually poor perfusion. Increases in the heart rate can also result in an increase in myocardial oxygen demand. This can be of particular concern in patients with coronary artery disease.

Finally, a prolonged elevated heart rate due to this arrythmia may eventually result in congestive heart failure. For the patient presenting with atrial fibrillation, there are two therapeutic options. One option includes restarting and maintaining sinus rhythm, known as rhythm control. The other option is allowing the patient to remain in atrial fibrillation but focusing on controlling the ventricular rate. This is known as rate control. Rate control can often be achieved with the use of beta-blockers or calcium channel blockers. If rate control is selected, patients are also started on anticoagulation medication for prevention of thrombus formation in the atrial appendage which can lead to ischemic stroke.

In those who are better candidates for the rate control strategy, control with traditional medications such as beta blockers and calcium channel blockers can be a challenge. Let's say you've tried a calcium channel blocker and then a beta blocker together. If the ventricular rate you are trying to achieve can't be reached with these medications alone, whether the heart rate just isn't responsive or the patient's blood pressure is too low for the patient to tolerate these medications, digoxin may be an appropriate option.

So, let's remind ourselves how digoxin works. Its mechanism increases the refractory period of conducting tissue and it has parasympathetic effects which results in a slowing the heart rate down but has little effect on the patient's blood pressure. Beta-blockers inhibit adrenergic receptors causing a reduction in heart rate and inotropy resulting in a reduction in cardiac output and blood pressure. Calcium channel blockers like diltiazem antagonize calcium channels resulting in arterial smooth muscle relaxation and ultimately a reduction in blood pressure.

As mentioned prior, digoxin not only results in a reduced heart rate, it also improves inotropy. It is because of this digoxin can be beneficial in select heart failure patients. In heart failure patients with a reduced ejection fraction or more specifically, systolic heart failure in contrast to diastolic heart failure, the primary issue is systolic dysfunction. Digoxin increases the intracellular calcium concentration and

results in improved contractility of the heart. While not first line therapy, digoxin can be utilized in appropriate patients to improve inotropy.

The effects of digoxin on mortality and morbidity in heart failure patients were investigated in the randomized, double-blind clinical trial performed by the Digitalis Investigation Group (DIG) in 1997. In the primary trial, patients with left ventricular ejection fractions of 0.45 or less were randomly assigned to a digoxin or placebo group, in addition to receiving diuretics and angiotensin-converting-enzyme (ACE) inhibitors. The results of the trial showed no significant difference in mortality between patients in the digoxin or placebo group; however, there was a reduction in the rate of hospitalization both overall and for worsening heart failure.

So, you may say digoxin seems like an excellent medication, why isn't it used more? On the surface, this medication seems like a medication with application in some of our sickest cardiac patients. Unfortunately, digoxin is notoriously difficult to dose and the risk of toxicity, even in the most skilled hands, is relatively high.

Digoxin has a narrow therapeutic index which makes close monitoring of digoxin levels of critical importance for patients. Patients must also be carefully selected.

Digoxin toxicity is a serious concern and it is critical we discuss this topic. It can emerge during long-term therapy as well as after an overdose. It can even occur when the serum digoxin concentration is within the therapeutic range. Specifically, for heart failure, the recommended range for serum digoxin concentration has been reduced over the past decade to 0.5 – 0.9 nanograms/mL. This updated range of serum digoxin concentrations is due to evidence of better outcomes at lower concentrations. With reference back to the DIG trial of 1997, further analysis was performed in 2003 to identify an association of serum digoxin concentration with outcomes in heart failure patients. The results of the trial showed that high serum digoxin concentrations were associated with increased crude all-cause mortality rates.

Toxicity can be seen in both acute and chronic presentations. Acute intoxication of digoxin may not show symptoms for several hours prior to the onset of a patient's symptoms. Abdominal pain along with nausea and vomiting as well as other vague GI issues are typically first symptoms. As toxicity continues, an exaggerated pharmacodynamic activity of the medication results in cardiac manifestations which may include bradycardia as well as AV blockage. However, tachyarrhythmias are also possible with Bidirectional Ventricular Tachycardia being nearly pathognomonic for digoxin toxicity. Patients may also become weak and confused. Typically, the severity of the patient's toxicity can be gauged by the degree of hyperkalemia (rather than the serum level of the drug alone).

As a reminder, the ATPase pump on cardiac cells works to increase intracellular potassium. When inhibited by the mechanism of digoxin, there is less potassium pumped into these cells which results in more extracellular (plasma) potassium. When the ATPase enzyme is excessively inhibited (as in digoxin toxicity), there is a resulting hyperkalemia.

For chronic cases of toxicity of digoxin are often seen in elderly patients who have been maintained on digoxin as an outpatient chronically. Often times this is due to one or several of the drug interactions of digoxin and/or declining renal function of the patient In patients on chronic diuretic therapy, volume depletion can alter the clearance of digoxin from the blood resulting in higher serum levels of the drug.

Of note, hypokalemia (which can be caused by many diuretics) can also place the patient at higher risk of toxicity. This is because digoxin binds to the same site of the ATPase pump as potassium. With lower potassium levels, digoxin binds more easily to the pump resulting in a more pronounced effect of the drug. The clinical presentation of patients presenting with chronic toxicity are vague, usually consisting of weakness, fatigue, confusion, and delirium.

The classic description of digoxin toxicity, seen commonly in standardized medical exams and textbooks includes viewing yellow-green halos around objects, a phenomenon called *xanthopsia*. This anomaly has been well-known since its discovery in the late 18th century. The paintings of the 19th century Dutch post-impressionist Vincent van Gogh were famous for their vivid colors, particularly the striking use of yellow, most evident in his later works such as *Still Life: Vase with Fifteen Sunflowers* and *The Reaper*. It is widely hypothesized, that the influence of yellow in such paintings are a result of the digitalis-induced xanthopsia that van Gogh may have during his life. It should be noted that typically non-specific visual disturbances are reported in chronic toxicity rather than the classic *xanthopsia*.

The treatment for clinically significant digoxin toxicity (hemodynamic instability, issues with mental status) is digoxin-specific antibody (Fab) fragments. If this treatment isn't immediately available, bradycardia can be treated with doses of atropine while life-threating ventricular arrhythmias should be approached according to the advanced cardiac life support algorithms. Blood pressure can be supported with fluid boluses (but obviously this must be done carefully in those with a history of heart failure.

We have now reached the end of this lesson on the cardiac glycoside, digitalis, and its derivative, digoxin. In proper hands Digoxin can be a useful medication for cardiac patients but can also be a dangerous one. When using digoxin, a clinician must be aware of its narrow therapeutic window and potential to induce toxicity with relative ease, especially in older more susceptible patients or those with end-organ impairments and metabolic derangements. Today, we also discussed the pharmacodynamics of digoxin, which will allow you to make sense of its use in applicable clinical scenarios. Thank you for listening and we hope you have learned a lot on this episode of Anesthesia Toolbox.

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