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Digoxin: The Art and Science

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ABSTRACT

The use of digoxin in the therapy of systolic heart failure and certain supraventricular tachycardias is controversial. This review of the art and science of digoxin presents information needed by physicians considering digoxin therapy for these common cardiovascular disorders.
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Following Withering's description of the use of foxglove for the therapy of "dropsy" in 1785, the use of digitalis glycosides has been the subject of innumerable articles, not only in medicine, but also in literature and art. For example, the numerous speculations that Van Gogh's yellowish view of the world that was at times reflected in his paintings was probably due to digitalis toxicity.

For over 2 centuries, the inotropic properties of the digitalis glycosides have been used in the treatment of chronic heart failure and its vagotonic properties to slow the ventricular response to certain supraventricular dysrhythmias. However, fewer pharmaceuticals have aroused more controversy than digitalis and its role in the management of cardiovascular disease.[1] Within the same medical training programs, house staff and cardiology fellows often have been given conflicting advice about the use of digitalis—everything from "You should never use the drug, it has no proven benefit; it is dangerous" to "Digitalis has a role in the therapy of systolic congestive heart failure and perhaps some atrial dysrhythmias, but before digoxin is prescribed, one must first appreciate the rather complex art and science of its use."[2]

There are ample reasons for concern, including the fact that digitalis toxicity is not only a medical emergency but also can be lethal!

Older cardiologists will remember the myriad of electrocardiographic complex "brady- and tachydysrhythmias" that were the result of digitalis excess. These complex dysrhythmias were used, not only in the training of cardiology fellows but also on cardiovascular board examinations. As trainees, we were often tested on our ability to interpret very complex dysrhythmias secondary to digitalis toxicity. And I have to admit, as a member of the American Board of Internal Medicine Subspecialty Boards of Cardiovascular Disease, we occasionally used electrocardiographic complex arrhythmias due to digoxin excess to help determine the certification of cardiologists in "Cardiovascular Diseases." Now, in clinical practice, these complex dysrhythmias secondary to digitalis excess should be extremely rare. One way to prevent them is to not use digitalis at all.

On the other hand, digitalis toxicity was and is almost always iatrogenic—due to the fact that the prescribing physician did not appreciate digoxin's rather complex pharmacology, a reason why many say that digitalis should not be prescribed. But in my view, digoxin may have a role in therapy in selected patients, but *only* if the prescribing physician is familiar with the art and science of digoxin use.

There do not appear to be as many dysrhythmias secondary to digoxin excess nowadays, perhaps because digoxin is used less in the treatment of heart failure or supraventricular dysrhythmias, and partly because those who use digoxin have made the effort to understand the art and science of its use.

My initial interest in digoxin was the result of my association as a house officer, cardiology fellow, and junior faculty with one of my mentors, Frank I. Marcus. Marcus had developed a technique to measure blood and urine concentrations of digoxin by using radioactive digoxin. We used this technique to study the pharmacokinetics of digoxin.

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DIGOXIN METABOLISM IN THE ELDERLY

One of my early academic publications was on digoxin metabolism in the elderly.[3] Tritiated digoxin (0.5 mg) was given intravenously to a group of elderly men (mean age, 77 years) and young men (mean age, 27 years). They were not in congestive heart failure. The serum creatinines of the old and young were not different; however, the creatinine clearance of the older group was about half that of the younger group, and the blood concentrations of digoxin were significantly higher in the elderly throughout the study ($P < .05$). In the elderly, the same dose of digoxin resulted in higher blood concentrations and longer blood half-life.[3] We concluded that this was due to the smaller body size and a diminished urinary excretion of digoxin in the elderly.[3]

CLINICAL SIGNIFICANCE

- The clinical benefits of digoxin are moderate, and the risks of toxicity are significant.
- A full understanding of digoxin's pharmacokinetics and the nuances of its clinical use are essential for anyone considering digoxin therapy.

DIGOXIN IN METABOLISM IN OBESITY

Another of our very early studies concerned digoxin's metabolism in obesity.[4] A single intravenous dose of tritiated digoxin was given to 5 obese patients before and after a mean loss of 102 pounds in weight! There were no significant differences in the blood concentration of digoxin before and after the weight reduction. There were no significant differences in the blood concentrations of digoxin when these data were corrected for fat-free body weight. The clinical implication of this study is that digoxin dosage may be erroneously high if calculated on the basis of total body weight in obese individuals.[4]

POOR CORRELATION BETWEEN PLASMA CONCENTRATION AND HEART RATE

Chamberlain et al were perhaps the first to find a poor correlation between plasma concentrations and the resting heart rate during atrial fibrillation.[5]

MEASURING SERUM LEVELS OF DIGOXIN

Two of the reasons that digoxin is so difficult to use are its very narrow window between therapeutic and toxic concentrations and its rather complex pharmacokinetics.[6] In most patients, digoxin is readily absorbed, but its blood levels are very high for the first few hours after administration because its distribution from the blood to the tissues takes a few hours.[7] Therefore, *digoxin should be administered at bedtime*, and the digoxin blood level should be measured in the mornings, in order to relate serum and digoxin tissue levels![6] The ideal (appropriately measured) serum levels of digoxin are in the range of 0.5 to 0.9 ng/mL. Digoxin toxicity is most likely to be present when the serum digoxin level is 1.2 ng/mL or greater. Because this orally administered drug takes time to reach a "steady state," the digoxin dose should be monitored by measuring the serum digoxin level in the morning, but only at least 1 week after beginning or alternating the dose of digoxin. The analysis should be repeated in 2 or 3 weeks after the patient has been taking a steady digoxin dose, again given at bedtime.[6]

DIGOXIN ABSORPTION IS VARIABLE

Another reason that digoxin serum levels need to be routinely measured at an appropriate time interval following the initiation of digoxin therapy is that, in about 10% of the population, orally administered tablets of digoxin are absorbed more slowly, and consequently, reach the distal intestines where digoxin is converted to cardioinactive reduction products by the intestinal bacteria.[8]

DIGOXIN THERAPY OF HEART FAILURE

"The beneficial effects of digoxin in patients in heart failure include reduced heart failure symptoms, improved NYHA [New York Heart Association] functional class ranking, increased maximal treadmill exercise time, modest increase in left ventricular ejection fraction, enhanced cardiac performance (eg, increased cardiac output and stroke work index), and decreased heart failure hospitalizations."[9] The Digitalis Investigation Group trial evaluated the effect of adding digoxin to an angiotensin-converting enzyme inhibitor and a diuretic, and found that digoxin significantly reduced hospitalizations and lowered the number of deaths attributable to progressive heart failure and produced no difference in all-cause mortality.[10]

Of concern, however, is that in some studies, digoxin therapy was associated with a trend toward an increased incidence of sudden (presumed arrhythmic) death.[10] A post hoc analysis of the sudden deaths suggested a relationship between mortality and plasma digoxin concentrations.[11] Specifically, digoxin concentrations > 1 ng/mL were associated with increased mortality risks.[11] My question is, would the results of this study have been different if the dose of digoxin had been given on the basis of lean body mass and not total body weight?[4] Again, if one is not committed to the proper use of drugs that have a narrow therapeutic index, such as digoxin, in my opinion, these drugs probably should not be used.

DIGOXIN'S PHARMACOKINETIC INTERACTIONS

Verapamil and quinidine increase serum digoxin levels considerably by decreasing the digoxin clearance. Certain antibiotics, such as erythromycin, increase serum digoxin levels by killing the gut bacteria responsible for digoxin hydrolysis.[12]

MECHANISM OF ACTION OF DIGITALIS

Digitalis binds to and inhibits the sodium-potassium ATPase pump, resulting in temporarily higher intracellular sodium concentrations, enhancing sodium calcium exchange and producing higher intracellular calcium concentrations.[2]

Digitalis's antiarrhythmic effects are predominantly via its indirect actions mediated by the autonomic nervous system and involve a vagotonic as well as a sympatholytic effect.[2] Although digoxin was used traditionally to slow the heart rate of ventricular response to chronic atrial fibrillation or flutter, heart rate should not be used as an indication for alternating digoxin dose! Because digoxin's heart rate slowing effect is via increased vagal tone, it only slows heart rate at rest. The patient's heart rate may be slow in the examining room, but with minimal exercise, the patient's heart rate may increase substantially despite therapeutic concentrations of digoxin. In such a patient's additional medications, usually, beta or calcium channel blockers are needed to control the patient's heart rate response to exertion.

This lack of digoxin effect and heart rate is because digoxin's heart rate slowing is only via increasing vagal tone. Thus, with the exercise, vagal tone decreases, and sympathetic tone increases, the patient's heart rate response to atrial fibrillation may become excessive. In this situation, a beta-adrenergic or calcium-channel blocker might be added to decrease ventricular response rate to atrial fibrillation. Again, if the blood level of digoxin is therapeutic, digoxin dose should not be increased!

DIGITALIS INTOXICATION: DIAGNOSIS AND THERAPY

The symptoms and signs of digitalis excess are often nonspecific. Nausea, anorexia, and dysrhythmias are well-known signs. Decreased strength, fatigue, and psychic disturbances are equally important but subtle symptoms of digitalis excess. The most common dysrhythmias are ventricular ectopic depolarization, heart block, junctional tachycardia, atrial-tachycardia with block, and ventricular tachycardia.

Digoxin toxicity can be reduced by physician education. Yet, during the nearly 3 centuries that digitalis glycosides have been available, its use should still be a major concern. Part of the previous increase in digoxin toxicity is probably related to the widespread use of potassium-wasting diuretics. This is less common now, but is another significant consideration.

CONCLUSIONS

The use of drugs such as digoxin that have a narrow therapeutic index requires not only an understanding of the drug's pharmacokinetics, and its advantages and disadvantages, but also the commitment by the prescribing physician to spend the extra time to not only understanding the complex pharmacologic therapeutics of digoxin, but also time in patient education before prescribing digoxin.

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