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Slow Down That Racing Heart: A Comparison of Ivabradine Versus Digoxin for the Treatment of Chronic Heart Failure

Lillian Smith[1], Juan Mosley[1]*, Megan Ford[2], Jonathan Courtney[2], Chase Stefanelli[2]

[1]Department of Pharmacy Practice, Florida A&M University, USA
[2]Florida Agricultural and Mechanical University, USA

Review Article

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***For Correspondence**

Juan Mosley, Assistant Professor of Pharmacy Practice, College of Pharmacy and Pharmaceutical Sciences, 153 W. Woodruff Ave, Crestview, FL, USA, Tel: (850) 689-4006, Fax: (850) 689-7870.

E-mail: juan.mosley@famu.edu

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ABSTRACT

Background: Heart failure (HF) is a chronic condition in which the heart cannot pump blood effectively enough to meet the demands of the body. Pharmacological treatment focuses on reducing the workload of the heart, reducing heart rate, increasing cardiac output, decreasing edema, and reducing mortality. Angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), aldosterone antagonists, and beta blockers are medication classes commonly used in the treatment of heart failure. Other treatment options include the use of digoxin and ivabradine.

Objective: Digoxin and ivabradine are both utilized to further reduce heart rate uncontrolled by the standard of care. However, digoxin and ivabradine differ based on mechanism of action, effect on left ventricular ejection fraction, drug interactions, costs, and adverse effects.

Discussion: Digoxin and Ivabradine have both been shown effective at lowering heart rate and treating some of the symptoms associated with chronic heart failure. Digoxin has been on the market longer, contributing to a more extensive knowledge of its safety and efficacy as compared to ivabradine. However, the SHIFT trial provides evidence that ivabradine can reduce hospitalizations. There are fewer drug interactions associated with ivabradine and drug level monitoring is not required. Nevertheless, ivabradine adverse effects may significantly impact heart failure patients.

Conclusion: Ivabradine is appealing with respect to its ability to reduce hospitalizations in patients with heart failure, as well as its ease of dosing and monitoring. However, due to its increased cost and lack of extensive use, digoxin may provide a more cost effective option for many patients.

INTRODUCTION

Heart failure (HF) is a chronic condition in which the heart cannot pump blood effectively enough to meet the demands of the body. This disease is widespread, affecting around 5.8 million people in the United States and more than 23 million people worldwide [1,2]. More men than women are affected, and African American individuals have a higher prevalence than those of other nationalities [1,3-5]. The incidence also increases with age since heart failure is often the result of other uncontrolled conditions, such as hypertension, coronary heart disease, heart valve disease, arrhythmias, and diabetes [6,7]. Other causes include congenital heart defects, previous myocardial infarction, and obstructive sleep apnea [7].

Heart failure is currently the leading cause of hospitalization among older adults, and annual expenditures in the U.S. exceed $10 billion dollars, making this disease especially burdensome to society [8]. However, according to the Heart Failure Society of

America, heart failure only receives 28.7 million dollars for research funding and affects roughly five million people, while lung cancer research receives 132 million and affects approximately 400,000 people [9]. Not only is heart failure financially burdening, it can also be associated with unpleasant signs and symptoms such as shortness of breath, chronic coughing, edema, weight gain, fatigue, lack of appetite, nausea, and increased heart rate [10].

Non-pharmacological treatment is dependent upon various lifestyle modifications. Patients should follow a healthy heart diet, reduce fluid intake to 1.5-2 liters, initiate weight loss and exercise, and cease from smoking [11]. If pharmacological treatment fails, patients can have a pacemaker or implantable cardioverter defibrillator (ICD) surgically implanted to maintain the heart's rhythm and rate. In addition, a left ventricular assist device can be inserted to help the heart to pump blood more efficiently through the body. A heart transplant is a last resort method of treatment; however, it is the only curative treatment available at this time.

Pharmacological treatment focuses on reducing the workload of the heart, reducing heart rate, increasing cardiac output, decreasing edema, and reducing mortality. Angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), aldosterone antagonists, and beta blockers are medication classes commonly used in the treatment of heart failure. Other treatment options include the use of digoxin and ivabradine, which are both utilized to further reduce heart rate uncontrolled by the standard of care. However, digoxin and ivabradine differ based on mechanism of action, effect on left ventricular ejection fraction, warnings, drug interactions, costs, and side effects. This article will discuss and evaluate those differences.

Digoxin

For over a decade there have not been any new pharmacological treatment options for symptomatic heart failure [12]. Digoxin has been the mainstay treatment for those patients who require additional treatment for the common signs and symptoms of heart failure. Digoxin is classified as a cardiac glycoside that works by a few mechanisms. First, Digoxin inhibits sodium-potassium ATPase, which leads to an increase in intracellular calcium concentration and an increase in contractility. Ultimately, this boosts the patient's left ventricular ejection fraction. Digoxin also sensitizes baroreceptors, making them more responsive to volume changes, and has vagomimetic action, meaning it mimics the effects of the vagus nerve [13]. The vagus nerve is part of the parasympathetic nervous system and innervates the sinoatrial and atrioventricular node leading to a slower heart rate. This cardiovascular effect allows digoxin to be used for rate control in atrial fibrillation as well. Finally, it causes neurohormonal deactivation by decreasing sympathetic response and decreasing renin-angiotensin system output. Although digoxin has a prominent role in the symptomatic treatment of heart failure, it also has drawbacks [13].

Digoxin has a narrow therapeutic index and requires frequent drug level monitoring. Drug levels are typically checked 6 hours after the last daily dose or immediately prior to the next scheduled dose. Therapeutic levels for digoxin are 0.5-2 ng/mL. Levels above 2 ng/mL are associated with toxicity that may include nausea, vomiting, abdominal pain, lethargy, bradycardia, and more severe effects such as heart block and hyperkalemia [13]. Digoxin toxicity can be caused by fluctuations in electrolyte concentration; therefore, electrolyte serum levels must be monitored closely. Treatment of toxicity characterized by visual and gastrointestinal symptoms can be treated by dose reduction; whereas more severe toxicity, conveyed most commonly as arrhythmias, often requires treatment with digitalis antibodies (digoxin immune Fab) [13]. However, if digitalis is unavailable, additional treatment options for toxicity include atropine, lidocaine or amiodarone.

Dosing digoxin presents additional difficulty due to the multitude of formulas. Digoxin dosing consists of a loading dose, maintenance dose, and accompanying formulas to calculate creatinine clearance, volume of distribution, and digoxin clearance [13,14]. These calculations are patient specific and differ based on kidney and liver function, age, steady state, and concurrent disease states [14]. Patients with heart failure and normal renal function are expected to reach steady state in 7-14 days and to have a volume of distribution of 6-7 L/kg. Patients with renal dysfunction may have a decreased volume of distribution (4-6 L/kg) and a longer time to steady state (15-20 days) [13]. An increased volume of distribution is seen in neonates, children, and patients with hyperthyroidism. Due to the time it takes digoxin to reach steady state, toxicity can occur before steady state levels can be obtained. Since Digoxin has a sensitive therapeutic index, a slight change in its absorption and clearance can result in toxicity or lack of efficacy. Additionally, each formulation of digoxin has a different bioavailability **(Tables 1 and 2).** These differences are accounted for by set factors that are used in the digoxin dosing formulas [14].

Table 1. Digoxin dosing formulas.

Volume of Distribution (Jusko Equation)	Vd = 226 + [(298 x CrCl) / (29.1 + CrCl)] x (BSA/1.73) • Vd = Volume of distribution (liters) • CrCl = Creatinine clearance (ml/min) • BSA = Body surface area (meters squared)
Loading Dose	LD = Vd x (Cp/F) ● LD = Loading dose ● Vd = Volume of distribution (liters) ● Cp = Target serum level (mcg/l) ● F = Bioavailability factor ● IV push = 1 ● Capsules = 0.95 ● Elixi r= 0.8 ● Tablets = 0.75

Clearance (Koda-Kimble)	Cl = [(A × CrCl) + B] × C ● Cl = Clearance ● A = 1 or 0.88 for Acute CHF ● B = 40 or 23 for Acute CHF ● C = Correction factor for other drugs ● Quinidine = 0.65 ● Spironolactone = 0.75 ● Verapamil = 0.7 ● Other = 0.71
Maintenance Dose	MD= (Cl X Cp × tau)/ F ● MD = Maintenance dose ● Cl = Clearance (liters/hour) ● Cp = Target serum level (mcg/l) ● Tau = Dosing interval (hours) ● F = Bioavailability factor
Steady State Trough Level	Cpss = (MD × F)/ Cl × tau) ● Cpss = Steady state trough level ● MD = Maintenance dose ● F = Bioavailability factor ● Cl = Clearance (liters/hour) ● Tau = Dosing interval (hours)

Table 2. Corlanor dose adjustment.

Resting Heart Rate (bpm)	Dose Adjustment
<50	Increase dose by 2.5 mg Max dose is 7.5 mg twice daily
50-60	Maintain current dose
60 or signs and symptoms of bradycardia	Decrease dose by 2.5 mg to the lowest dose of 2.5 mg twice daily. If the patient is currently at the lowest dose, then discontinue therapy

Drug interactions are a vital concern of digoxin therapy. Potassium depleting diuretics, such as furosemide and hydrochlorothiazide, can lead to digoxin toxicity and IV calcium may lead to arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone can block digoxin metabolism via p-glycoprotein, thus resulting in increased serum levels of digoxin. Drug interactions which cause decreased effectiveness of digoxin include antacids, kaolin-pectin, sulfasalazine, neomycin, and cholestyramine. These medications can inhibit digoxin absorption ultimately decreasing digoxin plasma concentrations [13].

The Digitalis Investigation Group trial (DIG) investigated the effects of digoxin on overall morbidity and mortality in patients with heart failure. Prior to this study in 1997, digoxin was primarily prescribed to patients with heart failure with the intention of improving contractility, cardiac output, and the mortality rate. However, at that time there was no long term evidence that digoxin improved these outcomes in patients with heart failure. This study involved sixty-eight hundred people that were randomized to either receive a median dose digoxin (0.25 mg/day) or a placebo. These patients had a left ventricular ejection fraction of <0.45, were diagnosed with heart failure, and were in normal sinus rhythm. Both groups could also receive an ACEI and diuretics while the study was being conducted. After a mean follow up time of 37 months, the study concluded that digoxin had no overall effect on mortality with comparable deaths rates between the two groups, but digoxin did reduce hospitalization visits associated with heart failure [15].

Overall, digoxin has been shown to be beneficial in the treatment of symptomatic heart failure. It has been studied extensively, and an abundance of clinical and pharmacokinetic data is available. Due to a long history of use, the cost of digoxin is more economic in comparison with newer brand name alternatives. Digoxin costs on average $34-$83 per 30 tablets (cash price). However, benefits of digoxin are sometimes overshadowed by the complexity of its implication in heart failure therapy.

Ivabradine (Corlanor)

Ivabradine (Corlanor) is the first medication in the drug class hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers. This medication acts primarily on the HCN channels of the sinoatrial node, selectively inhibiting the I_f current, thus reducing the spontaneous pacemaker activity and slowing the heart rate. Ivabradine does not have an effect on ventricular depolarization or myocardial contractility. Ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, which are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use [16]. A higher beta blocker dose may be inappropriate in patients who experience hypotension, fatigue, or dizziness. Contraindications to beta-blocker use include asthma, COPD, and 2nd or 3rd degree AV block [16]. In these patients, ivabradine is an advantageous addition to therapy.

In addition, this medication offers an improvement over heart failure treatment adjunct, digoxin, because serum drug levels

do not have to be monitored since ivabradine does not have a narrow therapeutic index. Instead, dose adjustments are based on the resting heart rate as shown in the following table [16].

Furthermore, ivabradine does not require dosing adjustments in patients with renal impairment as long as the creatinine clearance is >15 mL/min [16]. This is in contrast with digoxin where even slight renal insufficiency will require a digoxin dose decrease due to the reduction in excretion. Ivabradine and digoxin are both used to reduce hospitalizations associated with heart failure, although patients on digoxin may be hospitalized if their serum levels are not appropriately monitored. This risk is highest among elderly patients, who are more likely to have decreased renal function and decreased digoxin volume of distribution. Ivabradine would be more ideal in these patients because it does not carry the same risk of toxicity. **Table 3** shows complete comparison of Digoxin and Ivabradine.

Table 3. Comparison chart of Digoxin and Ivabradine

	Digoxin	Ivabradine
Uses	Atrial fibrillation, Heart failure	Chronic heart failure
Cardiovascular Effects	Negative chronotropic effect, Positive inotropic effect	Negative chronotropic effect
Dosage Adjustment Basis	Renal function, Liver function, Age, Steady state, Concurrent disease states	Resting heart rate, Renal function if CrCl <15 mL/min
Narrow Therapeutic Index	Yes; 0.5-2 ng/mL	No
Metabolism	P-glycoprotein substrate	3A4 substrate
Contraindications	Hypersensitivity to digoxin or other digitalis preparations, Ventricular fibrillation	Acute decompensated heart failure, Use with strong 3A4 substrates, Pacemaker dependent, Resting heart rate rate <60 bpm, Severe hepatic impairment, Severe hypotension, Sick sinus syndrome, Sinoatrial block, 3rd degree AV block
Adverse Effects	Nausea & vomiting, Dizziness, Mental disorder, Cardiac dysrhythmia, Sinoatrial block, Bradycardia Thrombocytopenia	Hypertension, Atrial fibrillation, Bradycardia, Luminous phenomena
Drug Interactions	P-glycoprotein inhibitors, P-glycoprotein inducers, Bile acid sequestrants, Sympathomimetics, IV calcium, K^+ depleting diuretics	3A4 inhibitors, 3A4 inducers, Negative chronotropes, Pacemaker (rate set ≤ 60 bpm)
Cost	$34-83/month	$450/month

According to the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT), the most frequent adverse effects associated with ivabradine in comparison with placebo include hypertension (8.9% vs. 7.8%), atrial fibrillation (8.3% vs. 6.6%), bradycardia (10% vs. 2.2%), and luminous phenomena (2.8% vs. 0.5%) [17]. The prevalence of these effects has not been established in practice; therefore, they may occur more or less frequently among the general population with heart failure. AF often coexists with heart failure, making this side effect of ivabradine even more troublesome. In addition, the prevalence of AF increases as heart failure becomes more severe. The frequency ranges from 5% among mild heart failure patients to 10-26% in patients with moderate heart failure, and occurs in up to 50% in patients with severe heart failure [18]. If patients with stable heart failure are started on ivabradine, it may lead to an even higher prevalence of AF among heart failure patients.

Ivabradine is a cytochrome P450 3A4 substrate and interacts with inducers and inhibitors of that metabolizing hepatic enzyme [19]. Moreover, ivabradine is contraindicated for use with strong CYP 3A4 inhibitors, such as clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole/lopinavir/ritonavir, nefazodone, ritonavir, and voriconazole [16]. This causes ivabradine therapy to be especially problematic in patients who are currently on therapy to treat HIV or have a fungal infection.

Ivabradine clinical trials

Numerous studies have been conducted to test the effectiveness of ivabradine and its purpose in heart failure. Even though it is the first member of a novel class, ivabradine has been compared with beta blockers and digoxin due to their similar effects. Ivabradine has been associated with positive outcomes, which led to its FDA approval in April of 2015.

One of the major studies investigating ivabradine was the SHIFT trial. This study was an international, randomized, placebo controlled trial in which 6505 heart patients participated and were followed for a mean duration of up to 42 months. The patients were allowed to be on additional beta blocker therapy and other medications. During this time, ivabradine was found to reduce cardiovascular risk or worsening of heart failure by up to 18%. Not only was this medication found to reduce risk for heart failure, it also reduced both hospitalization visits associated with heart failure and death by 26% [17].

Another main ivabradine study was the ivabradine for patients with coronary artery disease and left ventricular systolic dysfunction trial, also known as the BEAUTIFUL trial. This study was conducted internationally on a large scale involving 10,917 eligible patients and was randomized and placebo controlled. The primary endpoint was a composite of cardiovascular death, admission to the hospital for acute myocardial infarction, and admission to the hospital for worsening heart failure. Like the SHIFT study, the patients were allowed to be on beta blockers and additional drug therapy. In this study researchers concluded that

ivabradine was not effective in improving cardiac outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction, but could be used to reduce the incidence of coronary artery disease outcomes in a subgroup of patients that have a heart rate of 70 beats per minute or greater [20].

CONCLUSION

Digoxin and ivabradine have both been shown effective at lowering heart rate and treating some of the symptoms associated with chronic heart failure. There are advantages and disadvantages regarding the use of each. Digoxin has been on the market longer, contributing to a more extensive knowledge of its safety and efficacy as compared to ivabradine. However, the SHIFT trial provides evidence that ivabradine can reduce hospitalizations, which sets the stage for more trials to prove or refute this data [17]. There are fewer drug interactions associated with ivabradine and serum drug level monitoring is not required. Nevertheless, ivabradine adverse effects can have significant effects on heart failure patients.

While there have not been any trials performed directly comparing the use of ivabradine versus digoxin among patients with systolic heart failure; Ivabradine has been compared with digoxin using the SHIFT trial and the DIG trial. When examining these trials one can infer that ivabradine is a more potent bradycardic agent, but does not increase the left ventricular ejection fraction to as significant of a degree as digoxin. However, in the DIG trial there were more adverse events associated with the use of digoxin when compared to ivabradine in the SHIFT trial. Ivabradine was also found to have fewer drug interactions than digoxin as well [15].

In summary, ivabradine is appealing with respect to its ability to reduce hospitalizations in patients with heart failure, as well as its ease of dosing and monitoring. However, due to its increased cost and lack of extensive use, digoxin may provide a more cost effective option for many patients.

CONFLICT OF INTEREST STATEMENT

The authors of this manuscript report no conflicts of interest including, but not limited to, consulting fees, paid expert testimony, employment, grants, honoraria, patents, royalties, stocks, or other financial or material gain that may involve the subject matter of the manuscript.

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