ORIGINAL RESEARCH PAPER

General Medicine

ELECTROLYTE IMBALANCE IN HEART FAILURE PATIENTS USING IVABRADINE; A LONGITUDINAL STUDY CONDUCTED AT ONE OF THE CITIES OF NORTH INDIA

KEY WORDS: Electrolytes, Heart Failure, Ivabradine, NYHA Class

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ABSTRACT

Background: In heart failure, the mainstay therapy for congestion, is associated with electrolyte abnormalities and worsening of kidney function. Ivabradine mediates fluid retention in heart failure. In contrast to diuretics, the antagonist Ivabradine may increase net volume loss in heart failure without adversely affecting electrolytes and renal function. Subjects with heart failure may show hyponatremia, magnesium, and potassium (hypokalemia) deficiencies; the latter two play a pivotal role in the development of cardiac arrhythmias. **Material and Methods:** A total of 50 patients of age more than 18 years admitted with a clinical diagnosis of HF, evidenced by jugular venous distention, peripheral edema or rales, on standard therapy were included in the study and were treated with Ivabradine **Results:** There was a significant improvement in symptoms and New York Heart Association (NYHA) class after starting Ivabradine ($p \leq 0.05$). Increased thirst, dry mouth and increased urination were the common side effects observed among the patients. **Conclusion:** Ivabradine initiation in patients with HF in addition to standard therapy may hold promise in improvement in NYHA class. At the same time, we observed that serious adverse events such as renal function deterioration, and hypernatremia, hypermagnesemia or hyperkalemia developed after Ivabradine treatment.

Introduction

Heart failure (HF) is a condition that results when the heart is unable to provide sufficient blood flow to meet the body's metabolic demands. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define it as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood.[1]

HF is a major public health concern associated with a high prevalence and poor clinical outcomes. In the U.S., approximately 5 million people are affected, and more than 500,000 new cases are diagnosed each year.[2] HF is the leading cause of hospitalization among adults older than 65 years of age.[3] More than 1 million patients are hospitalized each year with a primary diagnosis of HF, accounting for a total Medicare expenditure exceeding $17 billion.[4] Despite dramatic improvement in outcomes with medical treatment, admission rates after HF hospitalization remain high, with more than 50.0% of patients re-hospitalized within six months of discharge.[3]

Pharmacological treatments of HF include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, diuretics, aldosterone antagonists, hydralazine/ nitrates, and digoxin. After undergoing "fast track" evaluation, ivabradine (Corlanor, Amgen) received Food and Drug Administration (FDA) approval in April 2015.[4] Ivabradine is indicated to reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with a left ventricular ejection fraction (LVEF) of 35% or less, who are in sinus rhythm with a resting heart rate of 70 beats per minute (bpm) or greater, and are either receiving maximally tolerated doses of beta blockers or have a contraindication to betablocker use.[5] Amgen obtained the American rights to ivabradine from Servier, which has been marketing the drug in Europe for approximately 10 years.[6]

Ivabradine is contraindicated in patients with acute decompensated HF, severe hepatic impairment, blood pressure below 90/50 mm Hg, a resting heart rate below 60 bpm prior to treatment, or pacemaker dependence (i.e., the patient's heart rate is maintained solely by the pacemaker). In addition, ivabradine is contraindicated in patients with sick sinus syndrome, sinoatrial block, or third-degree AV block unless a functioning demand pacemaker is present. As noted previously, the concomitant use of ivabradine and potent CYP3A4 inhibitors is also contraindicated.[5]

In the SHIFT study, the most common adverse events included bradycardia (10% for ivabradine versus 2.2% for placebo), hypertension (8.9% versus 7.8%), atrial fibrillation (8.3% versus 6.6%), and phosphenes (2.8% versus 0.5%). The following adverse events have been reported during post-approval use: syncope, hypotension, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment.[5]

The long-term efficacy and safety of ivabradine are not yet known. We hypothesized that Ivabradine is the only agent shown to clinically lower the heart rate without negative inotropism or effects on conduction and contractility. Consequently, ivabradine is not associated with the adverse events typically encountered with other bradycardic agents. The present study was conducted to assess the effects of ivabradine on HF patients and to recommend remedial measures.

Materials and Methodology:

This study was conducted in one of the medical colleges of Lucknow city. A total of 50 patients of age more than 18 years taking treatment (as out patient or in patient) for heart failure for 6 months of duration were included in this study. It was evidenced by jugular venous distention, peripheral edema or rales, on standard therapy were included in the study and were treated with Ivabradine.

Written proformas were filled up during inclusion of patients, which contained Demographic information (age, sex, occupation and place), questionnaires for risk factor evaluation (diabetes, drug history, malignancy, comorbid condition, hypertension etc.), information of clinical presentation (dyspnea, edema, etc.) and clinical signs. All patients received standard heart failure therapy, including diuretics, digoxin, ACEI/angiotensin II receptor blockers (ARB), BB, aldosterone blockers, hydralazine and/or nitrates, at the discretion of the treating physician daily weight monitoring was carried in all study patients. All enrolled patients according to our study protocol were treated with oral Ivabradine at doses of 15 mg daily for maximum 7 days or until discharge if ut was before 7th day of therapy. Patients were advised fluid restriction during the treatment for ADHF.

All patients had the following investigation performed after hospital admission;
1. Complete hemogram, fasting lipid profile, blood sugar, liver function test.
2. Renal function test (daily until discharge).
3. Serum electrolytes (daily until discharge).
4. Chest X-ray and electrocardiogram.
5. Echocardiography.

Statistical Analysis
All data was compiled at the end of the study and the sample was analysed with Chi-square. The $P < 0.05$ will be considered as statistically significant.

Observation/Results:
Electrolytes concentrations increased significantly after treatment with Ivabradine from baseline ($p<0.02$). There was a significant improvement in symptoms and New York Heart Association (NYHA) class after starting Ivabradine ($p\leq0.05$). Ivabradine significantly reduced the rates of cardiovascular death and HF hospitalizations in patients taking <50.0% of guideline-recommended beta-blocker dose. There was a dose related increase in urine volume, and a significant concomitant increase in sodium excretion at the two highest doses.

Side-effects associated with Ivabradine included increased thirst (24.0%), dry mouth (32.0%) and increased urination. 14.0% patients had worsening renal function and 12.0% patients developed hypernatremia.

Table 1: Baseline demographic and clinical profile of study patients

Parameters	No. of patients (n=50)		Percentage
Gender	Male	27	54.0
	Female	23	46.0
Mean Age (years)	68.2±13.6		
Hypertension		25	50.0
Diabetes		20	40.0
Previous myocardial infarction/IHD		30	60.0
Baseline NYHA classification	NYHA III	8	16.0
	NYHA IV	35	70.0
ADHF Aetiology	Ischemic	30	60.0
	DCM	15	30.0
	Valvular Heart disease	5	10.0
Heart Rate (>100 bpm)		40	80.0
Blood pressure (systolic blood pressure		30	60.0

Table 2: Comparison of clinical and investigational parameters between day of enrolment and at after Ivabradine therapy

Electrolytes	At the Enrolment (n=50)	After the Therapy (n=50)	p-value
Sodium (mEq/L)	121±3.2	136±3.0	<0.001
Serum urea (mg/dl)	21.4±12.1	26.6±14.7	0.088
Magnesium(m mol/L)	0.5±0.2	0.8±0.3	<0.001
Potassium (mmol/L)	3.1±0.4	3.7±0.5	<0.05
NYHA III/IV	43 (86.0%)	10 (10.0%)	0.046
Injection frusemide dose	80-100 mg	40-60 mg	

Table 3: Side effects of Ivabradine

Side effects	No. of patients (n=50)	Percentage
Thirst	12	24.0
Dry Mouth	18	32.0
Bradycardia	5	10.0
Hypernatremia	6	12.0
Hyper magnesia	4	8.0
Hyperkalaemia	4	8.0
Renal dysfunction	7	14.0
Nausea/vomiting	13	26.0

Discussion:
Ivabradine, is a HR-slowing drug,that inhibits the current in the sinoatrial node, unlike beta-blockers, has no known cardiovascular effects other than HR reduction. It was recently approved by the Food and Drug Administration for chronic HFrEF. The drug has also antianginal and anti-ischaemic properties in patients with stable angina.[7,8]

Subjects with congestive heart failure (CHF) usually show acid–base and electrolyte disorders, due both to the activation of several neurohumoral mechanisms and to drugs used in this condition, such as diuretics.[9] These abnormalities reflect the severity of CHF and contribute to the functional impairment and to the poor long-term prognosis.[10] The common electrolyte abnormalities are hyponatremia, hypokalemia, and hypomagnesemia. The acid– base disturbances generally observed are metabolic alkalosis pure or combined with respiratory alkalosis.[11]

In present study 50 patients who completed the study was compiled and analyzed where the mean age of the studied patients was 68.2±13.6 years with male predominance (54.0%) and other baseline characteristics mentioned in Table 1. Our findings were in accordance with the finding of Patra S et al[12] who studied short term efficacy and safety of low dose tolvaptan in patients with acute decompensated heart failure. The majority of patients hospitalized for ADHF have signs and symptoms of pulmonary congestion and followed by systemic congestion.[13] Hence, removal of excess fluid from either pulmonary or systemic bed represents a major treatment goal.

The symptomatic benefit exerted by Ivabradine has led to their wide clinical acceptance, even in the absence of efficacy and safety data from large randomized trials. However, this improvement can be associated with renal dysfunction, neurohormonal activation, electrolyte abnormalities, and hypotension.[14] Hence, there is a concern regarding the adverse impact of aggressive diuresis, particularly the impact on renal function and serum electrolytes, and this represents an important contributor to the frequent inadequacy of fluid management during hospitalization.[15]

In our study, the use of Ivabradine resulted in a mean reduction from baseline in the daily use of furosemide. However, it was statistically insignificant, which was in contrast to the previous studies.[16,17] Though there was a reduction in diuretics use, we found rising of blood urea after therapy with decrease serum creatinine, which was suggestive of pre-renal cause with intracellular dehydration due to excess free fluid dieresis with Ivabradine treatment.

In our study we observed serious adverse events such as renal function deterioration, and hypernatremia, hypermagnesia and hyperkalemia developed after Ivabradine treatment. A limited number of studies have shown the adverse effects of ivabradine such as visual disturbances, bradycardia, and atrial fibrillation.[18] In randomized clinical studies involving more than 3,500 patients and 800 controls, visual symptoms were reported in 17.0%, while sinus bradycardia of ≤ 55 bpm in 3.2% of all patients on 5 mg to 7.5 mg twice daily. Less than 1.0% of patients withdrew from therapy because of sinus bradycardia. Ivabradine showed no significant effects on QT interval. Due to the inhibition of the If channel, ivabradine can cause luminous phenomena (phosphenes). Inappropriate elevation of arginine vasopressin, which is seen in human with acute heart failure plays a key role in mediating water retention, contributing to both congestive symptoms and electrolyte imbalance.[19] Tolvaptan was effective most likely because of its impact on fluid balance.[20] Consistent with its mechanism of action, it influenced the primary end point mainly by reducing body weight and maintaining serum sodium, magnesium and potassium.[10] Hyponatremia occurs in 15.0-20.0% of hospitalized patients and constitutes a common serum electrolyte abnormality.[21] Hyponatremia and hypomagnesemia is reported to be an independent predictor of complications and death in patients with heart disease. So far, no trial has demonstrated mortality benefits of Ivabradine in acute heart failure. Findings of our study were also similar from the previous studies in these aspects.[22] The mean serum sodium, magnesium and potassium was significantly increased and hyponatremia, hypomagnesemia and hypokalcemia was corrected after starting oral Ivabradine. our patients significantly became asymptomatic after starting of Ivabradine. Above are the novel findings as there are no studied focusing on electrolytes imbalance in HF using Ivabradine drug.

It has been demonstrated that potassium depletion inhibits the reabsorption of magnesium in the distal convoluted tubule, thus leading to hypermagnesiuria and hypomagnesemia. However, it is well documented that primary disturbances of magnesium balance, particularly magnesium deficit, produce secondary cellular potassium depletion.[23]

In a randomized, double-blind, placebo-controlled trial of ivabradine in patients who had HFrEF (LVEF<35%), were in sinus rhythm with a heart rate ≥70bpm, had been admitted to hospital for heart failure within the previous year, and were receiving a -blocker at the recommended or maximum tolerated dose, an angiotensin converting enzyme (ACE) inhibitor (or an ARB), and/or a mineralocorticoid receptor antagonist, ivabradine significantly reduced the composite of cardiovascular death or hospital admission for worsening heart failure.[24]The study revealed that increased heart rate is a risk factor in patients with HFrEF in sinus rhythm, and lowering heart rate is an important target for treatment of heart failure.[25]

A maximal increase by 15 mEq/L was observed among patients with ADHF at the end of 7 days in an observational study performed in 40 patients.[12] Although it can be hypothesized that a higher dose of tolvaptan could have led to greater increase in sodium levels, earlier studies have not demonstrated a dose-dependent rise in sodium levels.[10] This finding is intriguing considering the fact that dose-dependent aquaretic effects have been observed in studies performed on healthy volunteers.[26] Nevertheless, this is a beneficial effect to avoid the development of hypernatremia.

Recommendations of the study

There are limited data on the long-term efficacy and safety of ivabradine. Most of the studies were small and did not have enough power. The potential teratogenic effects of ivabradine need to be assessed as many patients are women of reproductive potential. A further multicentre, randomized, placebo-controlled, double-blind study is needed for confirmation.

Conclusion

Heart Failure subjects develop multiple acid–base and electrolyte abnormalities due to several pathophysiological mechanisms. Their incidence is often correlated with the severity of cardiac dysfunction; furthermore, these imbalances are associated with a poor prognosis. Many of these metabolic derangements are drug-induced. Ivabradine initiation in patients with HF in addition to standard therapy may hold promise in improvement in NYHA class. At the same time, we observed that serious adverse events such as renal function deterioration, and hypernatremia, developed after Ivabradine treatment.

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