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SHORT COMMUNICATION

Initiation of ivabradine in cardiogenic shock

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Abstract

Aims Ivabradine is a selective sinus node inhibitor indicated in patients with symptomatic chronic heart failure on stable guideline-recommended heart failure therapy including appropriate doses of beta-blockers. The use in cardiogenic shock remains off label and has been considered a contraindication due to the theoretical risk of attenuating compensatory tachycardia. Tachycardia, especially in the context of inotropic therapy, may be deleterious, resulting in increased myocardial oxygen consumption and reduction in diastolic filling. As ivabradine does not have negative inotropic action, it may present a potential means to manage tachycardia in cardiogenic shock. We present a case series of four patients with cardiogenic shock started on ivabradine who were unable to tolerate beta-blockers.

Methods and results Five patients identified with cardiogenic shock defined as a severe reduction in cardiac index ($<$2.0 L/min/m^2) and elevated filling pressures on inotropic therapy were started on ivabradine in patients with sinus tachycardia [heart rate (HR) $>$100] who were intolerant to beta-blockers. Each patient had a cardiac magnetic resonance imaging, echocardiogram, and coronary angiogram for determination of aetiology. Invasive haemodynamics via pulmonary artery catheterization were measured during initiation and titration of ivabradine (baseline, 6, 12, 24, and 48 h after ivabradine administration) with continuous telemetry monitoring for any dysrhythmia or bradyarrhythmias. All patients tolerated ivabradine initiation, and at 24 h, an observed decrease in HR (106 ± 6.8 vs. 91.6 ± 6.4 b.p.m., P = 0.04), pulmonary arterial occlusion pressure (30.4 ± 4.8 vs. 24 ± 5.1 mmHg, P = 0.04), and right atrial pressure (16.8 ± 6.2 vs. 9 ± 4.3 mmHg, P = 0.0002). An improvement was observed in mixed venous oxygen saturation (SvO_2) (51 ± 8.8 vs. 64.8 ± 5.3%, $P < 0.04$), stroke volume (37.2 ± 7.6 vs. 49.2 ± 12.9 mL, $P < 0.04$), and right and left ventricular stroke work index (*Table 1*). No significant changes were observed with mean arterial pressure (73.4 ± 7.5 vs. 75.8 ± 5.0 mmHg, P = 0.81) and thermodilution-derived cardiac index (1.7 ± 0.2 vs. 2.5 ± 0.7 L/min/m^2, P = 0.58). Inotropic support was weaned successfully in three of five patients (88 ± 30 h) with subsequent titration of beta-blocker therapy. Two patients improved clinically but ultimately required left ventricular assist device implantation. All patients were discharged alive from hospital at 17 ± 7.9 days following ivabradine initiation.

Conclusions In our small non-randomized series of patients in cardiogenic shock, ivabradine was safely used to reduce HR in patients previously intolerant of beta-blockade. There are limited data surrounding the use of ivabradine in cardiogenic shock, and future studies should be undertaken to determine the optimal HR in humans with cardiogenic shock and whether systematic limitation of peak HR may improve outcomes.

Keywords Ivabradine; Cardiogenic shock; Heart rate; Heart failure; Vasopressor

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Introduction

Cardiogenic shock (CS) is a medical emergency characterized by decreased cardiac output and evidence of inadequate tissue perfusion taken in the presence of adequate cardiac filling pressures. Cardiogenic shock is frequently accompanied by tachycardia and commonly thought to be compensatory in nature. In the presence of cardiac ischaemia and/or structural heart disease, increasing heart rate (HR) leads to increased myocardial oxygen consumption demand and may result in

cardiac ischaemia and reduced contractility. However, currently used therapies (rate-limiting calcium channel blockers and beta-blockers) directly depress inotropy.[1]

Pressor therapy, administered to restore tissue perfusion pressure, may further drive tachycardia and contribute to clinical deterioration.

Ivabradine competitively blocks the IK_f channel (located only in the sinoatrial node) to reduce sinus HR through deceleration of the gradient of cellular diastolic depolarization without depressing myocardial contractility.[2] We report outcomes associated with the use of ivabradine to treat sinus tachycardia in a series of patients with CS confirmed by haemodynamic monitoring.[2]

Aims

We aim to evaluate the safety and tolerability of ivabradine for HR reduction in CS and whether limitation of peak HR may improve outcomes.

Methods

Five patients (four non-ischaemic and one ischaemic) with severe left ventricular (LV) dysfunction, CS, and sinus tachycardia were invasively monitored during treatment with inotropic and/or vasopressor therapy. Haemodynamic values and mixed venous gases were obtained at baseline, 12, 24, and 48 h.

Results

All patients tolerated ivabradine (*Table 1*) during the 48 h period. At 24 h after initiation (vs. baseline), we observed a reduction in HR (91.6 ± 6.4 vs. 106 ± 6.8 b.p.m., $P = 0.04$), pulmonary arterial occlusion pressure (24 ± 5 vs. 30 ± 4 mmHg, $P = 0.04$), and right atrial pressure (9 ± 4.3 vs. 17 ± 6 mmHg, $P = 0.0002$). An increase was observed in mixed venous oxygen saturation (SvO_2) (65 ± 5 vs. 51 ± 9%, $P < 0.04$), stroke volume (vs. 37 ± 8 mL vs. 49 ± 13 mL, $P < 0.04$), and right and LV stroke work index (*Table 1*). No significant changes were observed with mean arterial pressure or thermodilution-derived cardiac index. Inotropic support was weaned successfully in all five patients (88 ± 30 h) with subsequent initiation of beta-blocker therapy. All patients were discharged alive from hospital at 17 ± 7.9 days following ivabradine initiation.

Discussion

Cardiogenic shock is frequently accompanied by tachycardia thought to be compensatory for maintenance of cardiac output, despite the attendant increasing oxygen costs of work. This is thought to occur via two mechanisms: first, increased frequency of contraction (presumably at similar contractility) leading to a linear increase in cardiac output and, second, through an often-overlooked phenomenon, the Bowditch–Treppe effect.[3] This term describes the increased force of contraction that accompanies increased frequency of muscle depolarization. While this phenomenon describes the physiology in normal muscle, the opposite effect has been shown to occur in failing myocardium, where contractility may fall above HRs above 80–100 b.p.m. Early data were predominately derived via animal models; however, more recently, *ex vivo* and *in vivo* human data support an abnormal Bowditch–Treppe effect in humans with systolic LV dysfunction and increased rates of right ventricular pacing, worsening cardiac performance despite a 75% increase in HR.[3,4]

There is an abundance of evidence regarding HR reduction in chronic heart failure with beta-blockers, which demonstrate short-term reduction followed by a longer-term improvement in myocardial performance.[5] A case series of patients with severe LV dysfunction ($n = 10$) with pulmonary capillary wedge pressure ≥15 mmHg and sinus tachycardia experienced a 27% reduction in HR without any adverse effects following intravenous ivabradine.[6] Similarly, Porcile *et al.*[7] reported on 52 patients with decompensated heart failure (but not in shock) and sinus tachycardia during treatment with dobutamine reported a significant decrease in HR in association with increased stroke volume and without deleterious effects on CO or mean arterial pressure. In each of these studies, stroke volume rose in association with HR reduction as in our series. Indeed, our patients, in clinical and haemodynamic CS, were able to improve stroke volume, belying the notion of a 'fixed' stroke volume in the setting of sinus tachycardia. These benefits may be due to partial reversal of a negative force-frequency effect in the setting of severe LV systolic dysfunction, possibly in combination with a more favourable oxygen cost of myocardial work.

Ivabradine is well tolerated with a favourable side effect profile, which includes fatigue, symptomatic bradycardia, phosphenes, and a small increase in risk of atrial fibrillation but does not include negative contractility.[6] We observed no adverse events related to ivabradine in our case series with up to 1 year of follow-up. Although there are no randomized studies evaluating the use of ivabradine in CS, one prospective study aims to evaluate the use in patients with shock and multiple organ dysfunction syndrome not exclusive to cardiac dysfunction (NCT01186783).

In our small non-randomized series of patients in CS, ivabradine was safely used to reduce HR in patients

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Table 1 Patient characteristics and haemodynamic measurement at baseline and with the addition of ivabradine

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	49	52	46	29	54
LVEF (%)	15	21	24	16	17
Pressor type	Milnirone	Milnirone	Milnirone	Milnirone	Dobutamine
Pressor duration	48	96	120	Continuous	Continuous
ACEi or ARNI or ARB	Perindopril 4 mg	Enalapril 5 mg b.i.d.	Perindopril 4 mg	Perindopril 4 mg	Enalapril 2.5 mg b.i.d.
Beta-blocker	Carvedilol 3.125 mg b.i.d.	Carvedilol 3.125 mg b.i.d.	None	Carvedilol 3.125 mg b.i.d.	None
Nitrate	Nitro patch 0.4 mg	None	None	Nitro patch 0.2 mg	None
Diuretic	Lasix 40 mg daily	Lasix 40 mg b.i.d.	Lasix 40 mg daily	Lasix 80 mg b.i.d.	Lasix 20 mg
High-sensitivity troponin T (ng/L)	78	17	17	15	10 000
NT-proBNP (ng/L)	5938	6260	3975	4274	N/A
Disposition	Discharged in NYHA II status. Deceased pending primary prevention ICD	Discharged in NYHA II status on OMT	Discharged in NYHA II status on OMT	Currently NYHA IV discharged after VAD	Currently NYHA IV status after VAD

Parameter	Baseline (mean ± SD)	6 h (mean ± SD)	12 h (mean ± SD)	24 h (mean ± SD)	48 h (mean ± SD)	*P* value baseline vs. 6 h	*P* value baseline vs. 12 h	*P* value baseline vs. 24 h	*P* value baseline vs. 48 h
MAP (mmHg)	73.4 ± 7.6	74.2 ± 6.9	75.6 ± 5.4	75.8 ± 5.0	72.4 ± 8.7	0.96	0.89	0.81	0.58
HR (b.p.m.)	106 ± 8.2	99 ± 7.9	95.4 ± 8.0	91.6 ± 6.4	88.6 ± 6.1	0.64	0.23	0.04	0.004
SvO_2 (%)	51.0 ± 8.8	56.8 ± 8.8	63.4 ± 5.4	64.8 ± 5.3	66.6 ± 3.1	0.01	0.0003	0.00002	0.0000002
RAP (mmHg)	16.8 ± 6.2	10.8 ± 6.0	11.4 ± 5.9	9.0 ± 4.3	9.0 ± 4.9	0.004	0.007	0.0003	0.0003
PWP (mmHg)	30.4 ± 4.8	26.0 ± 4.9	23.0 ± 3.3	24.0 ± 5.1	23.8 ± 4.6	0.43	0.02	0.04	0.10
CI ($L/min/m^2$)	1.7 ± 0.2	2.1 ± 0.4	2.2 ± 0.4	2.5 ± 0.7	2.6 ± 0.5	0.98	0.94	0.62	0.58
RVSWI ($g{\cdot}m/m^2$)	5.4 ± 1.7	7.6 ± 3.0	7.2 ± 1.9	7.4 ± 2.8	8.0 ± 2.2	0.26	0.11	0.02	0.003
LVSWI ($g{\cdot}m/m^2$)	12.2 ± 2.5	13.8 ± 1.9	14.8 ± 3.6	16.4 ± 2.2	17.4 ± 2.8	0.71	0.12	0.02	0.0005
SV (mL)	37.2 ± 7.6	42.8 ± 9.2	46.0 ± 7.6	49.2 ± 12.9	56.2 ± 11.6	0.33	0.02	8.0×10^{-7}	6.6×10^{-12}
Lactate (mM)	2.42 ± 0.5	1.58 ± 0.6	1.44 ± 0.4	1.08 ± 0.4	0.96 ± 0.2	0.79	0.72	0.44	0.35
Creatinine (μmol/L)	137.8 ± 16.9	N/A	126.6 ± 16.7	119.2 ± 15.0	110.0 ± 18.0	N/A	0.08	3.3×10^{-4}	7.6×10^{-9}
Temperature (°C)	36.8 ± 0.5	37.0 ± .3	36.9 ± 0.1	37.0 ± 0.2	36.9 ± 0.1	1.00	1.00	1.00	1.00

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, cardiac index; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVSWI, left ventricular stroke work index; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OMT, optimal medical therapy; PWP, pulmonary wedge pressure; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SV, stroke volume; VAD, ventricular assist device.

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previously intolerant of beta-blockade. Future studies should be undertaken to determine the optimal HR in humans with CS and whether systematic limitation of peak HR may improve outcomes.

Conflict of interest

None declared.

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