Successful Combination of Landiolol and Levosimendan in Patients with Decompensated Heart Failure
A Report of 3 Cases

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Summary
Tachycardia and supraventricular tachyarrhythmias often impair cardiovascular capacity in patients with decompensated heart failure (dHF) treated with inotropes. Normalization of heart rhythm or rate typically improves diastolic filling and stroke volume (SV). Thus, isochronal administration of an ultra-short-acting and highly selective β1-blockers, such as landiolol, along with inotropic calcium-sensitizer medications, such as levosimendan, could benefit patients with dHF.

We present a case series of three patients with severe dHF and low ejection fraction who were successfully treated with a combination of landiolol and levosimendan. The co-administration of landiolol and levosimendan was well tolerated, improved cardiac function, normalized SV, and enabled the reduction of norepinephrine dosing in all patients. Additionally, the combination improved the vectorcardiographic spatial QRS-T angle and decreased the corrected QT interval. All patients were successfully discharged from the intensive care unit (ICU).

A combination of levosimendan and landiolol was safe and well-tolerated. This combination may be a new option for successful treatment of patients with acute dHF complicated by sinus or supraventricular tachycardias.

Key words: Critically ill, Cardiac tachyarrhythmias, Sepsis, Spatial QRS-T angle, Corrected QT interval

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Landiolol restores stroke volume (SV) in septic shock and decreases stroke volume variation, probably because of a decrease in the difference between maximum and minimum SV during breathing. Based on these actions, we can assume that a combination of a strong inotropic agent, such as levosimendan, and the ultra-selective β₁-blocker landiolol may improve cardiac hemodynamic function by increasing cardiac output (CO) via improved ventricular filling following the correction of heart rhythm and/or rate. In this study, we report cases of three patients treated with a combination of levosimendan and landiolol for severe shock with tachyarrhythmia.

Case Reports

In all cases, hemodynamic parameters were measured for all three presented patients, including this patient, using an EV 1000 platform (Edwards Lifesciences, Irvine, CA, USA) that also incorporates thermodilution. Spatial QRS-T angle and corrected QT (QTc) intervals were also automatically calculated in the same patients, by using a Cardiax computerized 12-lead electrocardiographic system (IMED, Budapest, Hungary), as previously described. The results of all measurements for all three patients, performed each morning for 5 serial days, are presented in Figure 1.

Case 1: A 70-year-old woman (78 kg) was admitted to the intensive care unit (ICU) with critical acute cardiac failure and left ventricular ejection fraction (LVEF) < 25% complicated by pulmonary edema. This case was included within a larger prospective observational study, performed at the First Clinic of Intensive Care at the Medical University of Lublin, Poland (KE-0254/172/2019). Patient was mechanically ventilated with FiO₂ 0.7 and PEEP + 10 cmH₂O. Ten days before admission to the ICU, she had undergone coronary artery bypass surgery (CABG) with extracorporeal circulation for acute coronary symptoms. Her comorbidities included hypertension and type II diabetes. The cardiac surgery was uncomplicated, and the patient required dobutamine infusion from the end of extracorporeal circulation to the 8 postoperative hour. Doses of dobutamine were gradually reduced from 7 μg/kg/min. The postoperative period was also without serious complications. A day before the admission into ICU, tachycardia with severe suffocation and rapid decrease in arterial oxygen tension to 58 mmHg were noted. The patient required oxygen supplementation with oxygen face-mask, and she was then intubated and mechanically ventilated with 70% oxygen. The patient was admitted into cardiac-postoperative intensive care and received an initial dose of amiodarone at 5 mg/kg/1 hour, continuing by 0.01 mg/kg/min. The norepinephrine infusion was started to maintain mean arterial blood pressure (MAP) between 60-70 mmHg. The treatment with amiodarone was unsuccessful. A coronary angiogram was performed just before admission to ICU and the presence of important disorders in blood flow were excluded. Hemodynamic measurements showed low cardiac index (CI) (Figure 1) with high extravascular water index (ELWI = 13.8 mL/kg). Systemic vascular resistance index (SVRI = 2776 dyne-sec/m²/cm²) was maintained with continuous norepinephrine infusion.
at 0.41 μg/kg/minute, with MAP being maintained between 60 and 70 mmHg. Laboratory measurements showed high plasma troponin I concentration (529 ng/L) and N-terminal fragment of prohormone B-type natriuretic peptide (NT-proBNP = 14,931 pg/mL). Immediately after admission to the ICU, the patient received an intravenous infusion of dobutamine at 9 μg/kg/minute. The dobutamine infusion did not improve CI, but increased tachycardia. Diuresis was maintained by continuous furosemide (Furosemide, Polfa, PI) infusion at 2.13 μg/kg/minute (120 mg/day). Controlled transesophageal echocardiography (TEE) showed that dobutamine did not improve cardiac function and worsened tachycardia. The electrocardiogram showed atrial fibrillation with a ventricular response rate of ~125 beats/minute. Intravenous infusion of levosimendan (Simdax, Orion Pharma, Fin) without an initial bolus was then started at 0.1 μg/kg/minute and continued at the same rate for 24 hours. At the same time, intravenous infusion of landiolol (Ranrapiq, Amomed, A) at 20 μg/kg/minute was started to restore cardiac rhythm. The landiolol and levosimendan infusions were well tolerated, and 1 hour after landiolol administration, sinus rhythm was restored and the heart rate decreased to 90 beats/minute and then to 75-80 beats/minute after 3 hours. The treatment with landiolol was continued with metoprolol (BetaLoc ZOK 100, AstraZeneca, USA) administered orally at 100 mg/day. During the first 24 hours, the combined therapy resulted in a net negative 24-hour fluid balance (~1250 mL) that enabled a progressive reduction in the dose of norepinephrine (Figure 1). The patient’s clinical condition noticeably and progressively improved during the 5 consecutive days. Controlled TEE showed improved cardiac contractility with an LVEF of >30% and decreased ELWI (7.2 mL/kg). Plasma NT-proBNP decreased to 210 pg/mL, and no cardiac arrhythmias were observed after the combined levosimendan and landiolol therapies were terminated. The patient was extubated on day 7 and discharged to the cardiology department on day 13 of ICU admission. After 3 weeks, she was discharged to cardiology sanatorium.

**Case 2:** A 76-year-old man (71 kg) with a history of myocardial infarction was treated for septic shock following massive pneumonia. His comorbidities included hypertension and mild chronic heart failure assessed as New York Heart Association (NYHA) class II. He was admitted to our hospital’s pulmonology service with severe dyspnea and fever. Four days after admission, episodes of atrial fibrillation with a high ventricular rate (Figure 1) complicated by hypotension (88/54 mmHg) were noted and he was transferred to the ICU. Immediately after admission to the ICU, he was intubated and mechanical ventilation was started with FiO2 0.6, PEEP + 7 cmH2O. According to Surviving Sepsis Campaign guidelines and after a check of fluid responsiveness, fluid resuscitation was applied to restore vascular volume deficiency. Hemodynamic parameters measured by the EV 1000 platform showed a low CI (Figure 1), ELWI = 12.1 mL/kg and SVRI = 1745 dyne·s·m−2·cm−5, such that continuous infusion of norepinephrine at 0.85 μg/kg/min was then commenced. Microbiologic cultures from the blood, bronchoalveolar lavage, and urine were obtained and empirical antibiotic therapy was started. Based on KIDIGO criteria, acute kidney injury with anuria was diagnosed and continuous renal replacement therapy was started. Laboratory studies showed high plasma procalcitonin concentration (PCT = 32 ng/mL), high NT-proBNP (6520 pg/mL), and leukocytosis (WBC = 17,200/mL). Transthoracic echocardiography showed global impaired cardiac contractility with an LVEF of ~20%. Based on clinical symptoms and hemodynamic findings, intravenous infusion of levosimendan at 0.1 μg/kg/minute was started without initial bolus and continued at the same rate for 24 hours. At the same time, intravenous infusion of landiolol at 10 μg/kg/minute was started to restore cardiac rhythm. Both were well tolerated, and 2 hours after the beginning of the infusions, the heart rate decreased to 75 beats/minute with restored sinus rhythm (Figure 2). During the first 24 hours, the combination therapy again progressively enabled reduction in the dose of norepinephrine. The treatment with landiolol was continued with metoprolol at 100 mg/day. Daily fluid balance was “zero” after 24 hours of treatment. The patient’s clinical condition was progressively improved. Daily fluid balances were negative for the next 5 consecutive days (from ~1000 mL to ~2400 mL) and diuresis returned on day 4 of renal replacement therapy, which was discontinued on day 6 of treatment. The patient was extubated on day 16 of treatment and discharged to the pulmonology department on day 24 days of admission to the ICU. He returned home on day 30 of admission into ICU.

**Case 3:** A 66-year-old woman (95 kg) was admitted to the ICU with acute respiratory failure following dHF with an LVEF of < 20%. The electrocardiogram showed a supraventricular arrhythmia with a heart rate of 113 beats/minute (Figure 1) and ventricular ectopy. Four days before the ICU admission, she had been admitted to the orthopedic department with a fracture of the femoral neck. Her comorbidities included obesity, hypertension, dyslipidemia, type II diabetes, and chronic heart failure assessed as NYHA III. Her cardiovascular problems had begun in 2010 when a coronary angiography revealed notable coronary artery disease and two stents had been placed. She was then frequently hospitalized for recurrent episodes of atrial fibrillation. On the day of admission to the ICU, acute decompensated heart failure was diagnosed, and she was intubated for severe dyspnea with peripheral desaturation to 78%. In the ICU, she was mechanically ventilated with FiO2 0.45 and PEEP + 7 cmH2O. Hemodynamic parameters were measured by EV 1000 platform, with thermodilution showing a low CI (Figure 1). SVRI was maintained with continuous norepinephrine infusion at 0.3 μg/kg/minute. Laboratory studies showed high plasma NT-proBNP (20,328 pg/mL) and troponin I (159 ng/L). Immediately after admission to the ICU, she received an intravenous infusion of dobutamine at 10 μg/kg/minute. Continuous furosemide infusion at 1.76 μg/kg/minute (120 mg/day) was also used to obtain a negative fluid balance of ~1500 for 24 hours and ~750, ~1000, and ~1000 for the next 3 consecutive days, respectively. Controlled TEE showed that dobutamine did not improve cardiac function and only worsened tachycardia. Intravenous infusion of levosimendan was then started at 0.1 μg/kg/minute without initial bolus and continued at the same rate for 24
Figure 2. Serial 12-lead electrocardiograms 5 min before the beginning of landiolol and levosimendan administration and just after treatment completion. Landiolol and levosimendan were infused continuously for 24 hours.
hours. At the same time, an intravenous infusion of landiolol at 20 μg/kg/minute was started to restore the cardiac rhythm. The landiolol and levosimendan infusions were well tolerated. After 24 hours, although sinus rhythm was not restored, the ventricular response rate decreased to 60 beats/minute, and the combination of levosimendan and landiolol again allowed for a reduction in the dose of norepinephrine. Similar to previous cases, the treatment with landiolol was continued with an oral dose of metoprolol. CI slightly improved 24 and 48 hours after the beginning of levsimendan and again decreased on the day 3 in part due to decreased heart rate to 50 beats/minute. Based on hemodynamic findings and tendency to bradycardia, metoprolol was discontinued and a continuous dobutamine infusion was started at 5 μg/kg/minute. After this period, a small dose of norepinephrine was used to maintain mean blood pressure > 70-80 mmHg. The patient’s clinical condition slowly improved and tracheostomy was performed on day 14 after intubation. Controlled TEE showed persistent atrial fibrillation but with a better controlled ventricular response rate. LVEF assessed on day 10 was 28%, with accompanying mild mitral valve insufficiency and CI of 2.9 L/minute/m². The plasma Nt-proBNP decreased to 505 pg/mL. Mechanical ventilation was discontinued on day 24 and the infusion of norepinephrine on day 26. She was discharged to rehabilitation with symptoms of hypotensive delirium, without full contact on day 34. She breathed via tracheostomy with inactive oxygen supplementation.

Discussion

To the best of our knowledge, this is the first report documenting the successful combination of levsimendan and landiolol in critically ill patients treated for severe cardiac dysfunction with tachycardia and impaired CO. In the first two patients, the combination of these medications spectacularly improved cardiac function and restored SV, which enabled a reduction in the infused dose of norepinephrine. In the third patient, the combination of levsimendan and landiolol enabled the restoration of hemodynamic stability, but with only slow improvement in the clinical condition, possibly due in part to the persistence of atrial fibrillation. Additionally, the concurrent administration of landiolol with levsimendan reduced spatial QRS-T angle and shortened the QTc interval in all cases, while being safe and well-tolerated.

Tachycardia significantly limits cardiovascular capacity in patients with severe LV dysfunction and dHF by decreasing diastolic filling and increasing myocardial oxygen consumption. Tachycardia itself increases the ionic abnormalities in myocytes, particularly intracellular Ca²⁺ handling, impairing LV contractility and contributing to LV dysfunction. Several studies have documented that severe tachycardia per se or tachycardia with atrial fibrillation worsens LV function and increases mortality and morbidity in patients with dHF. Currently, therapeutic options for patients with heart failure and tachycardia suggest the use of β-blockers to restore or maintain sinus heart rhythm, or to decrease the ventricular response rate in chronic atrial fibrillation. Landiolol is a highly effective β-blocker for controlling heart rhythm without any vasodilatory effect because it is ultra-short-acting and quickly metabolized. Moreover, landiolol in combination with milrinone improves intracellular Ca²⁺ handling in cardiomyocytes, which may improve LV function. An increase in SV, via improved ventricular filling during normal heart rhythm, can also improve cardiac function. In all the presented cases, landiolol effectively reduced the ventricular response rate or heart rate and thereby likely contributed to increased SV index and CI. In the early phase of experimental lipopolysaccharide endotoxemia, landiolol increases SV in association with decreases in heart rate without any decrease in CO. In the present report, the second patient was treated for sepsis-related cardiac dysfunction and the highest increase in stroke volume index (SVI) resulted from landiolol treatment. However, the increase in SVI and CI was still presumably driven mainly by levsimendan rather than landiolol administration.

Levosimendan increases cardiac contractility via a positive inotropic and slightly positive chronotropic effect, which may promote tachycardia. Hence, some authors have suggested the combined use of levsimendan with β-blockers. A combination of levsimendan with esmolol improves CI in association with a decrease in HR in critically ill patients with tachycardia treated for cardiogenic shock. Use of β-blockers frequently results in rapid hypotension due to mechanisms connected with their negative inotropic activity and blockade of vascular β-receptors. In the presented cases, a selective blockade of β-receptors by landiolol did not affect vascular tension, and improvement of CO via increased ventricular filling and cardiac contractility allowed for maintenance of blood pressure with a reduced dose of norepinephrine.

A combination of landiolol and levsimendan also reduced the spatial QRS-T angle and shortened the QTc interval. Increased spatial QRS-T angle and QTc interval are well-known risk factors for life-threatening cardiac arrhythmias. An increase in cardiac contractility improves cardiac function particularly in patients with QRS duration < 120 ms. Notably, improved cardiac function is associated with narrowing of the spatial QRS-T angle. β-blockers also shorten QTc while being the mainstay in prevention and treatment of cardiac arrhythmias associated with prolonged QTc interval. Landiolol reduces QTc interval, thus reducing the risk of cardiac arrhythmias during induction of anesthesia. In all our patients, the spatial QRS-T angle decreased and QTc interval shortened following landiolol and levsimendan infusion. Moreover, we did not observe any life-threatening cardiac arrhythmias in these patients. However, the effect of levsimendan and landiolol, as well as their combination, on the spatial QRS-T angle and QTc interval should be statistically documented further studies.

Finally, the combination of levsimendan and landiolol improved CO and SV with enabling a reduction in the infused dose of norepinephrine in all the three patients. The combination of landiolol and levsimendan improved cardiac hemodynamic function and corrected the heart rhythm, thereby reducing risk of life-threatening cardiac arrhythmias reflected by QTc and spatial QRS-T an-
gle in patients with dHD. Based on our observations, we suggest that the combination of levosimendan and landiolol may be a promising new option for patients with dHD complicated by tachycardia who do not respond to dobutamine treatment. Additionally, this combination may be successfully used in patients with a high risk of cardiac arrhythmias in whom the use of inotropic medications intensified tachycardia without CO restoration. However, these promising hemodynamic effects require further validation in follow-on studies involving a larger sample size.

Disclosure

Conflicts of interest: None.

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