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Tolvaptan to achieving high urine output and avoiding hyponatremia in covid-19 with adhf patient:case report

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Abstract

Pandemic of Coronavirus Disease 2019 (COVID-19) is a world health problem, with rapidly growing infected subjects. Recently, hyponatremia has been found to be associated with increased morbidity and mortality in hospitalized patients with severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV2) pneumonia. On the other hand, Acute heart failure (AHF) is a leading cause of hospitalization and readmission in the US. The standard management of AHF is removing the fluid primarily with loop diuretics or ultrafiltration. Unfortunately, the loop diuretics could lead to electrolyte imbalance.

Case Description: A Male 71 years old with confirmed COVID-19 came to emergency room with shortness of breath and history of coronary artery disease (CAD). Unfortunately, the infection leads patient to non-ST Elevation Myocardial Infarction (NSTEMI). During the treatment, patient down to acute decompensated heart failure (ADHF). The congestion did not respond to Furosemide 40mg intravenously and Spironolactone 25mg orally.

Discussion: Arginine- vasopressin (AVP) levels are elevated in heart failure. AVP acts via V2 cause fluid retention and hyponatremia. Aquaretic (i.e., Tolvaptan) are antagonists of AVP-2 receptors in the renal tubules to promote solute-free water clearance and correct hyponatremia.

Conclusion: Important to avoid hyponatremia to prevent mortality and sepsis in patient COVID-19.



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Introduction

Pandemic of Coronavirus Disease 2019 (COVID-19) is a world health problem, with rapidly growing infected subjects. The number of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) cases is rapidly growing [1]. However, acute coronary syndromes (ACS) are still a major cause of morbidity and mortality worldwide and should not be overshadowed in this era, especially because of the physiopathological links between ACS with SARS-CoV-2 infection [2].

On the other hand, Acute heart failure (AHF) is a leading cause of hospitalization and readmission in the US. Worsening dyspnea is the most common reason for hospitalization, which is largely a result of sodium and water retention-related fluid overload. The standard management of AHF is removing the fluid primarily with loop diuretics or ultrafiltration. Arginine vasopressin levels are elevated in heart failure. It results in myocardial fibrosis/hypertrophy and vasoconstriction by activating V1a receptors. Water retention and hyponatremia are mediated thru activation of V2-receptors. In heart failure, vasopressin antagonists prevent progression of left ventricular dysfunction [3,4,5,6].

Hyponatremia and hypernatremia (dysnatremia) also have been found to be associated with increased mortality in hospitalized patients in general, as well as specifically in patients admitted with community-acquired pneumonia (CAP). Dysnatremia is associated with mortality, sepsis, or intensive therapy (IT) in patients hospitalized with SARS-CoV2 pneumonia. So that, there are challenges associated with effective diuresis and not to mention possible adverse effects [7,8]. We reported case COVID-19 with Acute Decompensated Heart Failure (ADHF) Profile B *et causa* (ec.) Non-ST Elevation Myocardial Infarct with challenges fluid retention.

Case Illustration

A male 71 years old came to emergency room (ER) with shortness of breath for three days and getting worsen in the last one day before. The shortness of breath not getting better with change of position and felt continuously all day. Before the shortness of breath come, patient having dry cough and fever for 7 days. Patient also felt fatigue and anosmia for last 7 days. Patient confirmed COVID-19 with RT-PCR since 7 days before came to hospital and already took medicine such as Azithromycin 500mg once daily for five days, N-Acetylcysteine

200mg three times a day, Vitamins D3 once daily and Vitamins B Complex once daily. The patient had been vaccinated with Sinovac two times and the last dose in 3 months before. His wife and daughter also hospitalized with confirmed case of COVID-19 one week before. Patient has medical history of coronary artery disease and takes medicine such as Clopidogrel, Bisoprolol, and Simvastatin.

On physical examination, patient *compos mentis*, blood pressure was 126/60 mmHg, pulse rate 108 beats/minutes regularly, respiration rate 24 times/minutes with 96% of oxygen saturation via room air, the body temperature 37,7°C. Jugular vein pressure (JVP) PR±2cm. From thorax auscultation was S1S2 single, regular, no murmur, no rhonchi and no wheezing. Warm and no edema.

From other examination, electrocardiography (ECG) examination found sinus tachycardia with 108 beats/minutes (bpm) regular. On chest x-ray thorax-PA found cardiomegaly with cardio thoracic ratio (CTR 56%) and consolidation in paracardial right lung, infiltration in parahilar left lung, increased broncho vascular pattern both lungs that conclude bronchopneumonia bilateral. Laboratory test shown erythrocyte (RBC): 4,09.10⁶/uL, hemoglobin (HGB): 12,3/dL, hematocrit (HCT): 36,9%, platelet (PLT): 178.10³/uL, leucocyte (WBC): 9,57.10³/uL, neutrophil: 8,83.10³/uL, lymphocyte: 0,6.10³/uL with neutrophil and lymphocyte ratio (NLR): 14,71. Blood chemistry analyzed troponin I: 0,02ug/L, creatinine (SC): 0,95mg/dL, D-Dimer 300ng/mL, natrium (Na) 136 mmol/L, kalium (K) 3,6 mmol/L, random blood sugar (RBS) 148mg/dL, RT-PCR COVID 19 positive SARS-CoV2.

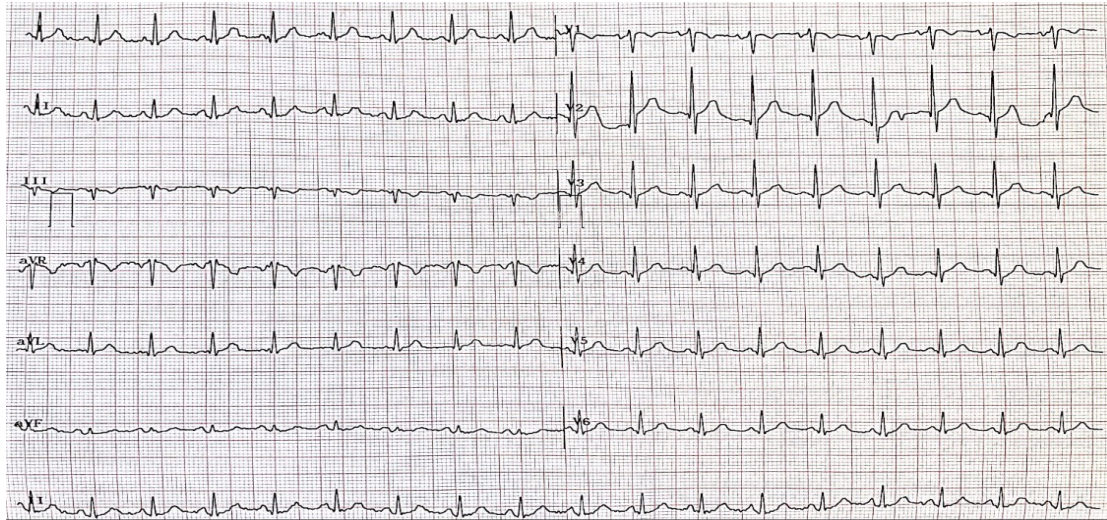


Figure 1. ECG

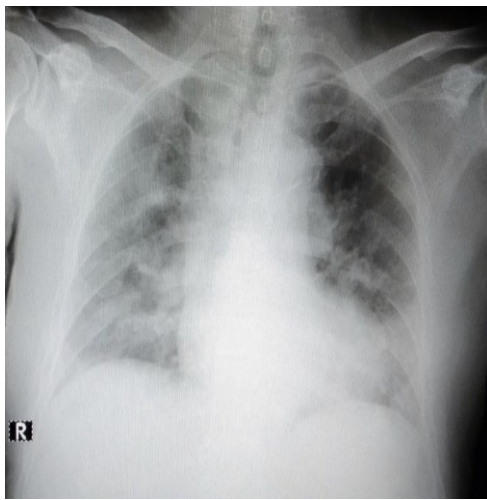


Figure 2. Chest X-Ray

Patient diagnosed with Confirmed Case COVID 19 with moderate symptom, pneumonia bilateral, and NSTEMI. Thus, patient treated with oxygen nasal cannula 3lpm, intravenous fluid drip (IVFD) normal saline 20 drops/minutes, intravenous Levofloxacin 750mg once daily, Paracetamol 1000mg four times per day, and pantoprazole 40mg twice daily. Subcutaneous Fondaparinux 0,25mg once daily, Oral Favipiravir 1600mg twice daily orally on first day then 600mg twice daily orally until seven days, Loading Aspirin on first day 160mg then 80mg once daily, Clopidogrel 75mg once daily, Bisoprolol 1,25mg once daily, Atorvastatin 40mg once daily, Cilostazol 100mg twice daily, Vitamin D3 5000mg once daily, and Zinc 80mg once daily.

After three day of treatment, the patient's condition deteriorated to Confirmed Case COVID 19 with moderate symptom, Pneumonia Bilateral, ADHF Profile B ec NSTEMI and Hypoalbuminemia. Patient oedema in both extremities and sleepless. The blood pressure was 147/90 mmHg, pulse rate 100 bpm, respiration rate 20 times/minutes with 96% of oxygen saturation via room air, the body temperature 36,7°C. Jugular vein pressure (JVP) PR±2cm. From thorax auscultation was S1S2 single, regular, no murmur, no rhonchi and no wheezing. Warm but oedema on both lower extremities. The albumin serum level is below normal limit in 3g/dL and slightly increased d-dimer level to 400ng/mL. Patient given additional therapy intravenous Ceftriaxone 2gr once daily, Furosemide 20mg once daily, Fartison 100mg once daily, oral Spironolactone 25mg once daily, increased Bisoprolol to 2,5mg daily, Diazepam 5mg once daily, and Vip Albumin once daily. The next day patient felt palpitation and the pulse rate was 95 bpm. Thus, Bisoprolol dose increased to 3,25mg once daily.

Day 10 of hospitalization, SpO₂ down to 85%, d-dimer level increased to 1300ng/mL, kalium serum down to 3,2mmol/L but natrium still in normal limits. Patient remained fever and cough. Unfortunately, the shortness of breath is getting worsen and the lower extremities remained oedema but warm in palpation. Patient diagnosed with COVID-19 Moderate Symptom, Pneumonia Bilateral, ADHF Profile B ec NSTEMI, High Risk VTE, Hypokalemia. Patient got additional treatment oxygen supply increased to 15lpm via non rebreathing mask (NRM), intravenous Meropenem 1gr three times daily, Ciprofloxacin 400mg once daily, Furosemide 40mg once daily, and KSR twice daily orally. The next day, kalium remained

decreasing until 2,9mmol/L, thus, patient given additional treatment with KCl 50meq drip. Post drip the kalium serum elevated to 3,4mmol/L.

Day 16 of hospitalization, patient became Acute Lungs Oedema. Cough was decreased but the shortness of breath remained with rales on both lungs and oedema lower extremities. The patient was given Tolvaptan 2mg once daily. After one day of given Tolvaptan 2mg, urine output was 3700cc/24h and no remain rales on the lungs. The SpO2 was getting better, thus, we tapering down the oxygen supply. After 21 days of being hospitalized, patient discharged with better condition. No remained shortness of breath and oedema extremities.

Discussion

We reported a case of male aged 71 with Pneumonia ec COVID-19 Confirmed Case COVID 19 with moderate symptom, Pneumonia Bilateral. Patient had a history of CAD. Unfortunately, the level of Troponin I was elevated. Thus, patient diagnosed with NSTEMI. Recently, COVID-19 known could lead to ACS by Angiotensin Converting Enzyme 2 (ACE2) mediated SARS-CoV-2 enters into the lung alveolar epithelial cell and host cell. ACE2 is also spread widely in human heart, and vessels. Infection of endothelial and pericytes could lead to microvascular and microvascular dysfunction. Cytokine storm, increasing interleukin (IL)-6, IL-7, IL-22, and CXCL10 may leading to atherosclerosis plaque instability or rupture and contributing to development of acute coronary events [1].

After three days of being threatened, patient condition down to ADHF ec NSTEMI with oedema extremities. Thus, patient given daily Furosemide 40mg intravenously and Spironolactone 25mg orally. The initial approach to congestion management involves i.v. diuretics with the addition of vasodilators for dyspnea relief if blood pressure allows. To enhance diuresis or overcome diuretic resistance, options include dual nephron blockade by loop diuretics (furosemide or torasemide) with thiazide diuretics or natriuretic doses of MRAs [3,6].

Day 10 of hospitalization, SpO2 down to 85%, d-dimer level increased to 1300ng/mL, kalium serum down to 3,2mmol/L but natrium still in normal limits patient became Acute Lungs Oedema. Furosemide increased dose to 40mg intravenously. Day 16, Cough was decreased but the shortness of breath remained with rales on both lungs and oedema lower extremities. The natrium serum was 138mmol/L and kalium was fluctuated between 3,1—3,4mmol/L. Patient's electrolyte was fluctuated due to infection and diuretics. Patient given additional Tolvaptan 2mg orally. Vasopressin antagonists such as tolvaptan block the action of arginine vasopressin (AVP) at the V2 receptor in renal tubules and promote aquaresis [5,6]. Tolvaptan may be used to treat patients with volume overload and resistant hyponatremia. On the treatment we must to achieving high urine output outright avoid hyponatremia over the duration of diuretic therapy [4]. Thus, we decided to add Tolvaptan on the standard therapy by 2mg once. Tolvaptan, an oral V2 antagonist (30-90 mg once daily) added to standard therapy for patients hospitalized with worsening heart failure, decreased body weight, increased urine output, and increased serum natrium by approximately 4 mEq/L from approximately 138 mEq/L [5].

Goyfman M et. al in found treating AHF by achieving high urine output with combined therapy furosemide, metolazone, and spironolactone, with tolvaptan, while maintaining stable electrolytes and creatinine in a short period to euvolemic state, is safe. There were minimal fluctuations in serum electrolyte levels and serum creatinine over the duration of diuretic therapy. There was no statistically significant change in patients' creatinine from immediately prior to therapy to the last day of therapy [4].

HOPE-COVID-19 registry reported from 4664 patients RT-PCR-confirmed SARS-COV2 pneumonia and a registered admission serum natrium level were analyzed. Death occurred in 988(21.2%) patients, sepsis was diagnosed in 551 (12%) and IT in 838 (18.4%). Hyponatremia was present in 957/4,664 (20.5%) patients, and hypernatremia in 174/4,664 (3.7%). Both hyponatremia and hypernatremia were associated with mortality and sepsis [7].

Among the observed side-effects of Tolvaptan treatment, dry mouth was most common (40%), followed by nausea, vomiting (35%), thirst (30%), abdominal pain (20%) and muscle cramps (15%) of study patients. One interesting observation after starting Tolvaptan treatment was that 10% (4/40) patients developed hypernatremia and 15% (6/40) patients developed renal dysfunction during Tolvaptan therapy [5,9]. Patient's OUP increased to 3700cc/24hr and no remain rales on the lungs. The side-effects of Tolvaptan in this patient was thirst.

Conclusion

Vasopressin antagonists such as tolvaptan block the action of arginine vasopressin (AVP) at the V2 receptor in renal tubules and promote aquaresis. Tolvaptan, an oral V2 antagonist (30-90 mg once daily) added to standard therapy for patients hospitalized with worsening heart failure, decreased body weight, increased urine output, and increased serum natrium. Combined therapy furosemide, metolazone, and spironolactone, with tolvaptan, while maintaining stable electrolytes and creatinine in a short period to euvolemic state, is safe.

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