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Case Report
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Prolonged First-Dose Hypotension Induced by Sacubitril/Valsartan

Fu-Chih Hsiao[1,2] and Pao-Hsien Chu[1,2,3]

Entresto was recommanded by major guidelines as the frontline therapy for heart failure with reduced ejection fraction since its clinical benefit was proved by the PARADIGM-HF trial. Angiotensin converting enzyme inhibitors are the cornerstone of the treatment of HF. Varying incidences of first-dose hypotension have been reported and recognized as a potential limiting factor for prescribing. According to previous reports, the onset of hypotension mostly occur 3-5 hours after the first dose. However, the pattern of entresto-related hypotension has not been reported. We present a case of HF, who had delay onset (about 8 to 18 hours) and prolonged (3 to 6 days) first-dose hypotension. Further investigation is required to illustrate this phenomenon.

Key Words: First dose • Hypotension • Sacubitril/valsartan

INTRODUCTION

Sacubitril/valsartan was recommanded by major guidelines[1,2] as the fronteline therapy for heart failure with reduced ejction fraction (HFrEF) since its clinical benefit was proved by the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial.[3] In this trial, sacubitril/valsartan resulted in more symptomatic hypotension than enalapril. Enalapril and other angiotensin converting enzyme inhibitors, one of the cornerstones of evidence-based therapy for HFrEF,[4] were reported to be associated with variable incidence of first-dose hypotension in heart failure patients without definite mechnism.[5-8] In contrast, the pattern of sacubitril/valsartan-related hypotension is not well illustrated. Here we have presented a case of prolonged hypotension after having the first dose of sacubitril/valsartan.

CASE REPORT

A 74-year-old male with anterior wall ST segment elevation myocardial infarction in 2012, who received percutaneous coronary intervention 4 hours after symptom onset. Angiography demonstrated thrombotic occlusion at proximal left anterior descending artery. Thrombosuction, followed by drug-eluting stent deployment were performed uneventfully with final thrombolysis in myocardial infarction flow grade 3 (TIMI-3). Risk factors for coronary artery disease included smoking and hyperlipidemia. Heart failure with left ventricular ejection fraction (LVEF) 35-40% developed after the first insult. Long-term candesartan (4 mg/day), bisoprolol (1.25 mg/day), and eplerenone (50 mg/day) were prescribed regularly in office. Compared to the average dosage of major trials, the dosages of above medications remained relatively low due to borderline office blood pressure (BP). Although followed the guideline-directed medical therapy, serial echocardiography showed

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[1]Division of Cardiology, Department of Internal Medicine; [2]Heart Failure Center; [3]Healthcare Center; Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan.
Corresponding author: Dr. Pao-Hsien Chu, The Cardiology Division, Department of Internal Medicine, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, No. 199, Tun-Hwa North Road, Taipei 105, Taiwan. Tel: 886-3-328-1200 ext. 8162; E-mail: taipei.chu@gmail.com

left ventricular adverse remodeling and deterioration of LVEF to 25-30%. The patient suffered from multiple episodes of decompensation and hospitalization between 2014 to 2016 (Figure 1A). Cardiac resynchronization therapy was not indicated because of narrow QRS on electrocardiography (Figure 1B).

Low dose sacubitril/valsartan (sacubitril 24.25 mg + valsartan 25.75 mg) was first prescribed in 2016 at office since the patient remained symptomatic (functional class III) despite having stable dosage of beta-blocker, angiotensin receptor blocker (ARB), and minerocorticoid receptor antagonist (MRA). Diuretics was not required and euvolemic status without jugular vein engorgement nor peripheral edema was documented. Although euvolemic clinically, this patient may have subclinically mild volume and salt depletion according to blood urea nitrogen/creatinine ratio and hyponatremia. The latest office BP before having sacubitril/valsartan was 85/52 mmHg, but the home BP is above 95 mmHg after reconfirmed. He visited emergent department 18 hours after having the first pill due to dizziness and general weakness. BP 68/36 mmHg was recorded in the triage, accompanied with acute renal failure (Figure 1C). Hypotension persisted despite fluid challenging, so dopamine was infused and continued for total 6 days before hemodynamics sstablized and renal function returned to baseline. To reassure the tolerability, same dose of sacubitril/valsartan was given one week later under monitoring in hospital. At the time, the patient was in euvolumic status and did not have any other medication. However, hypotension was recoreded 3 hours later (Figure 1D), which again requiring dopamine infusion for 3 days to support hemodynamics. One of the possiblity might be a vasovagal response triggered by dehydration. Beta-blocker, ARB, and MRA were given after hypotension subsided and he was discharged.

DISCUSSION

Soon after the publishment of PARADIGM-HF trial,[1] heart failure guidelines of both Europe and North America put sacubitril/valsartan as class I recommendation for the treatment of HFrEF due to its remarkabe benefit clinically. In this tiral, patients in the sacubitril/valsartan group (14%) were more likely than those in the enalapril group (9.2%, $p < 0.001$) to have symptomatic hypotension, but these events rarely required the discontinuation of treatment. In a post hoc analysis by Verdeny et al.,[9] hypotension events required hospitalization were more common in the enalapril group (12.3%) than in the sacubitril/valsartan group (7.5%, $p < 0.001$). This study also demonstrated that participants with hypotension

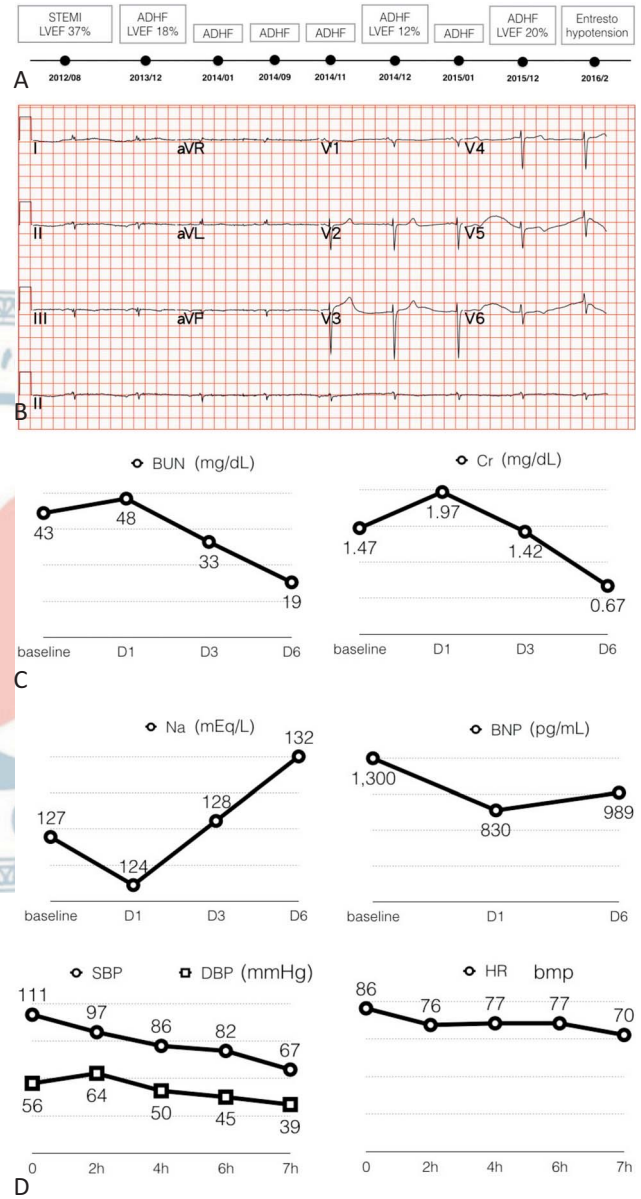

Figure 1. *(A) Clinical course during 2012 to 2016. ST segment elevation myocardial infarction (STEMI), left ventricular ejection fraction (LVEF), acute decompensated heart failure (ADHF). (B) Baseline electrocardiography. (C) Renal function, sodium (Na), and B-type natriuretic peptite (BNP) before and after having first puill of sacubitril/valsartan. (D) Hemodynamics change after having sacubitril/valsartan in hospital.*

during run-in period derived similar benefit as those who did not experience hypotension.

In concordance with guidelines' recommendation and the post hoc analysis, we prescribed sacubitril/valsartan to a patient, who tolerated ARB with borderline baseline BP. However, unexpected prolong hypotension occurred at the first time and by rechallege. The exact onset of hypotension was more reliable on rechallege during hospital. As Figure 1D illustrated, BP began to drop 2-3 hours and peaked at 7 hours after having the pill. The onset time was compatible with the pharmacokinetics of sacubitril/valsartan, of which valsartan, sacubitril, and the active metabolite LBQ657 reached the peak plasma concentration within 1.6-4.9, 0.6-0.9, and 1.8-2.7 h after the dose.[10] However, the unusual long duration of inotropics infusion of the present case was not compatible with the pharmacokinetics, that is valsartan, sacubitril, and LBQ657 have mean elimination half-lives of 9.9, 1.4, and 11.5 hours.[10] One possible explanatino is that the clinical physician was reluctant or too slow to stop inotropics due to borderline BP, which may be asymptomatic as baseline office BP.

There were some risk factors for sacubitril/valsartan-related hypotension in the present case. First, Hodsman et al.,[11] reported that a greater blood pressure reduction was observed in patients with renin-dependent states, such as low sodium intake and dehydration. In addition, Verdeny et al.[9] reported that age (odds ratio 1.15 per 10 years older), HF diagnosis > 5 years (odds ratio 1.24), implanted cardioverter defibrillator (odds ratio 1.54), statins (odds ratio 1.32), oral anticoagulants (odds ratio 1.3), and nitrates (odds ratio 1.26) are independent predictors for hypotension event.

In conclusion, according to the result of PARADIGM-HF trial, post hoc analysis, and guidelines, hypotension is not a reason to avoid sacubitril/valsartan. The patients with dehydration, older age, or longer history of HF, might result in hypotension, and should start low dosage (50 mg twice daily). Moreover, BP should be monitored closely not only in the first hour, but within one day.

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