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CASE REPORT | LIVER

Terlipressin-Associated Complete Heart Block

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ABSTRACT

Terlipressin has been recently approved in the United States to treat hepatorenal syndrome, a feared complication of both acute and chronic liver diseases. Side effects of the medication have been studied through clinical trials and the precedent use in Europe, as well as extrapolation from its analog vasopressin. As its use is becoming more prevalent, unforeseen complications have arisen. We report a case of complete heart block associated with terlipressin use in presumed hepatorenal syndrome in acute liver injury.

KEYWORDS: Terlipressin; hepatorenal syndrome; complete heart block; acute liver injury

INTRODUCTION

Hepatorenal syndrome (HRS) is a deadly cause of acute kidney injury in persons with liver disease, which is attributed to the accumulation of hepatically cleared vasodilatory substances in the splanchnic circulation, leading to low systemic vascular resistance and reduced renal perfusion.[1-3] HRS typically occurs in advanced cirrhosis but can also occur as a complication of acute liver injury (ALI) or failure.[3]

Terlipressin is a synthetic analog of vasopressin, a hormone that constricts vessels by activating V1 receptors of vascular smooth muscle cells in the splanchnic and systemic vasculature.[4] This medication was approved in Europe several years ago and in the United States in 2022 for treating HRS.[5,6] In the CONFIRM trial, terlipressin with albumin resulted in significantly higher reversal of HRS (32% vs 17% with albumin only).[6] Its use has been associated with improved renal replacement therapy-free, transplant-free, and all-cause mortality over 3 months but with increased adverse events, commonly gastrointestinal (abdominal pain, nausea, and diarrhea) and more rarely respiratory failure and associated mortality.[6-8] Common cardiovascular side effects include hypertension and reflex bradycardia, and few cases of unstable bradycardia, ventricular tachycardia or arrhythmias, and myocardial infarction have been reported.[7,9-14]

In this study, we report a case of a patient who developed complete heart block (CHB) after receiving terlipressin for presumed HRS, requiring immediate chronotropic intervention.

CASE REPORT

A 70-year-old woman with metabolic syndrome (elevated body mass index, hypertension, type 2 diabetes, and hyperlipidemia) without a known liver or cardiac disease was transferred to our institution for the management of ALI from hepatitis B infection. Her course at the local hospital was notable for shock that briefly required vasopressors (attributed to splanchnic vasodilation from ALI) and acute kidney injury (creatinine [Cr] up to 3.4 mg/dL from baseline 1.1 mg/dL) attributed to hypotension-related acute tubular necrosis. Her clinical status and liver chemistry tests initially improved then worsened again while on entecavir.

On transfer, history was notable for no recent alcohol use, new medications, supplements, herbs, or travel. Examination was notable for severe jaundice, anasarca, and normal mental status. Laboratory testing showed the following: Cr 3.9; aspartate transaminase

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186 U/L, alanine transaminase 133 U/L, alkaline phosphatase 269 U/L, total bilirubin 35.2 mg/dL, direct bilirubin 35.2 mg/dL; international normalized ratio 1.6; and hepatitis B virus DNA 5,810 IU/mL (from 843,000 IU/mL prior). Additional workup was unremarkable for other viral (hepatitis A virus/hepatitis C virus/hepatitis D virus/hepatitis E virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus), autoimmune (Anti-smooth muscle antibody, Immunoglobulin G, anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies, anti-phospholipiase A2 Receptor, C3/C4), or alcohol-related (phosphatidylethanol) etiologies. Imaging demonstrated heterogeneous liver parenchyma, splenomegaly, and small-volume ascites, raising a concern for cirrhosis. Transjugular liver biopsy revealed portal and lobular inflammation consistent with infectious hepatitis, along with portal fibrosis (Ishak stage 3), and hepatic venous pressure gradient of 5 mm Hg.

Over 2 weeks, the patient developed oliguric renal failure with anasarca and Cr rise to 4.7 mg/dL. Urine sediment was bland, and urine sodium was below the detection limit (<20 mmol/L); the serum Cr did not improve with albumin infusion, midodrine and octreotide. The review of her electrocardiograms (ECG) revealed right bundle branch block (RBBB) without bradycardia or arrhythmia. After a multidisciplinary discussion, a time-limited trial of terlipressin was initiated for presumed HRS.

After 0.85 mg of terlipressin administration on the floor (+0:00 hour), the patient's heart rate decreased from 87 to 27 bpm (+3:28 hours) (Figure 1). Blood pressure dropped to 75/40 mm Hg, and the patient became less responsive. A rapid response was called, and 2 doses of 1 mg atropine were administered without a sustained response. Epinephrine and dopamine infusions were started, and the patient was transferred to the cardiac intensive care unit where she experienced vital sign (46 bpm and 128/53 mm Hg; +4:07 hours) and mental status recovery. The review of echocardiogram showed RBBB that progressed to bifascicular block with widened PR and QRS intervals, followed by CHB (Figures 2 and 3). A temporary pacing wire was placed (+4:57 hours) for a target ventricular rate of 60 bpm. Her native rate exceeded 60 bpm at +6:06 hours when ECG showed resolution of CHB. The QRS returned to baseline by approximately 8 hours after terlipressin administration, and the first-degree atrioventricular block block resolved by 20 hours.

Vasopressors were weaned off, and the pacing wire was removed several days later. Transthoracic echocardiogram showed no significant abnormalities. The serum Cr eventually improved over few weeks, and her liver function tests continued to improve on entecavir.

DISCUSSION

Terlipressin is associated with cardiovascular complications including hypertension, bradycardia, and rarely arrhythmias and ischemia.[10-14] Although stable sinus bradycardia is commonly seen, only one incidence of unstable bradycardia has been reported.[9] In this study, we report CHB associated with terlipressin in which the patient developed CHB then experienced a spontaneous resolution 6 hours after the medication administration, coinciding with the half-life of terlipressin.

The mechanism behind the development of CHB following terlipressin administration is unclear. This patient had an underlying RBBB, and the abnormal conduction system may have

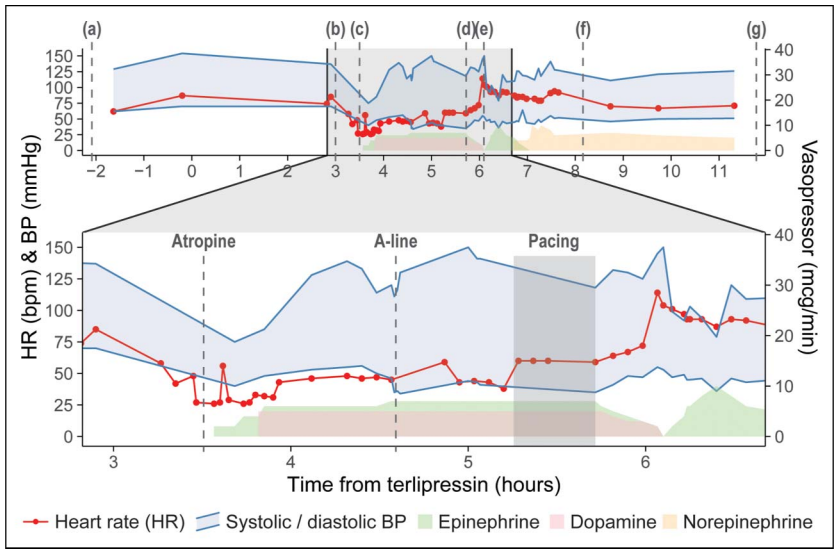

Figure 1. Vital sign changes in response to terlipressin injection. Time of terlipressin injection is marked at 0:00 hour. Heart rate (HR) and blood pressures (BP) are shown with respect to the left y-axis and vasopressor infusions (epinephrine, dopamine, and norepinephrine) with respect to the right y-axis. Gray vertical dotted lines in the graph above (A–G) indicate corresponding ECGs in Figure 2. Gray dotted lines in the graph below indicate atropine injections (1 mg at +3:28 hours and 1 mg at +3:30 hours) and arterial line insertion (+4:34 hours). Period of pacing with temporary transvenous pacing wire at 60 bpm is shaded in gray (+5:14 to +5:43 hours).

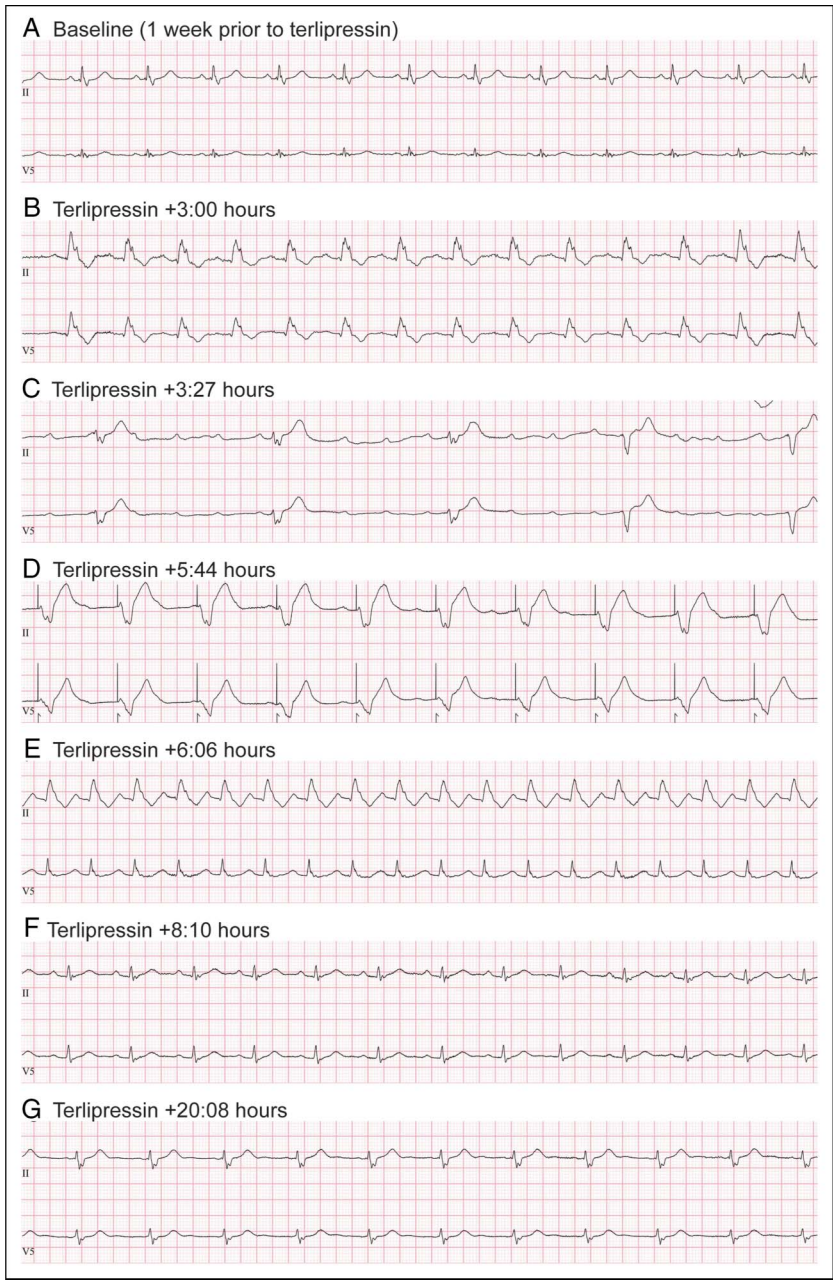

Figure 2. Evolution of ECGs in response to terlipressin injection. Full ECGs are available in Figure 3. Rhythm strips (leads II and V5) are shown here to highlight (A) sinus rhythm with right bundle branch block at baseline, (B) prolongation of PR and QRS intervals at +3:00 hours, (C) complete heart block at +3:27 hours, (D) ventricular pacing at 60 bpm at +5:44 hours, (E) resolution of complete heart block at +6:06 hours, (F) resolution of QRS prolongation at +8:10 hours, and (G) resolution of PR prolongation at +20:08 hours.

been susceptible to increased parasympathetic tone that reflexively followed terlipressin-induced vasoconstriction or from sensitization of central baroreceptors by terlipressin as Yartsev et al discuss.[9] Alternatively, terlipressin may have acted directly on the conduction system to cause CHB. In rabbit pulmonary vein cardiomyocytes, vasopressin increased late Na^+ currents and Ca^{2+} leak from the sarcoplasmic reticulum (SR), in keeping with V1 receptor function in activating Ca^{2+} release from the SR.[15] Increased Ca^{2+} leak is typically associated with tachyarrhythmias rather than conduction delays, and class IC antiarrhythmic agents, such as flecainide (which can cause various degrees of atrioventricular block block including CHB), work partially by reducing Ca^{2+} release from the SR.[16-18] Therefore, terlipressin resulting in a conduction delay is an unexpected outcome. Increasing evidence suggests that terlipressin may be a nonselective vasopressin analog with V2 and V3 agonism, which may differentially affect Ca^{2+} leaks in various cell types.[19] Therefore, further studies to evaluate the effect of terlipressin on the conduction system are warranted.

The approval of terlipressin has opened new doors for treating HRS, but it may be accompanied by serious complications such

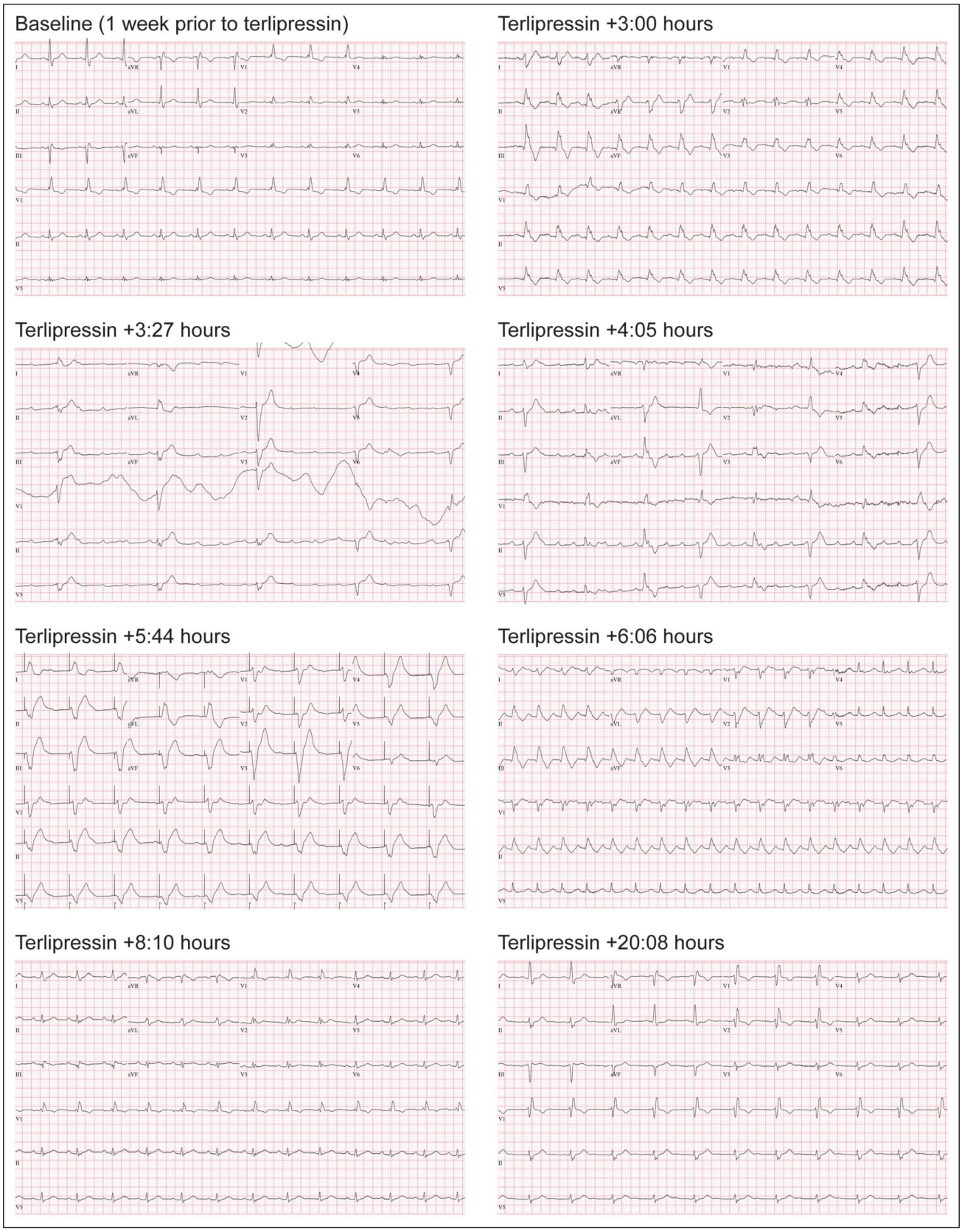

Figure 3. ECGs before and after terlipressin injection.

as respiratory failure and unstable rhythm. Based on this report, we recommend additional caution for the use of terlipressin in individuals with underlying conduction abnormalities. To mitigate this risk, we recommend a baseline 12-lead ECG and cardiac telemetry when initiating terlipressin.

DISCLOSURES

Author contributions: All authors participated in the conception, acquisition, analysis, and interpretation of data and contributed to the drafting and reviewing of the manuscript and figures. J. Song is the article guarantor.

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