

Terlipressin-Induced Peripheral Cyanosis in a Patient with Liver Cirrhosis and Hepatorenal Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 65
Final Diagnosis: Terlipressin-induced peripheral cyanosis
Symptoms: Cold extremities
Medication: Terlipressin
Clinical Procedure: Terlipressin administration was discontinued
Specialty: Gastroenterology and Hepatology

Objective: Challenging differential diagnosis

Background: Hepatorenal syndrome (HRS), which is a type of functional renal impairment, is one of the most serious complications in patients with liver cirrhosis. Terlipressin can induce splanchnic vasoconstriction, which increases the renal blood flow and has beneficial effects on HRS. However, terlipressin administration may cause serious ischemic complications such as skin ischemia, peripheral gangrene, and ischemic bowel necrosis. Here, we report a case of peripheral cyanosis following terlipressin administration in a cirrhotic patient with HRS.

Case Report: The patient was a 65-year-old male. He was considered to have type-1 HRS, and thus, terlipressin was administered. However, peripheral cyanosis involving the fingers, toes, area around an umbilical hernia, and scrotum was noted. Thus, terlipressin administration was discontinued. Subsequently, his condition rapidly improved.

Conclusions: We reported a case of peripheral cyanosis following terlipressin administration, which resolved after discontinuation of terlipressin administration. It is important to recognize the early signs of side effects and discontinue the administration of the suspected drug immediately.

MeSH Keywords: Hepatorenal Syndrome • Liver Cirrhosis • Paracentesis

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Background

Liver cirrhosis has become one of the major causes of morbidity and mortality worldwide. The Global Burden of Disease Study reported that over a million people died from cirrhosis in 2010 worldwide, compared with only 676 000 deaths in 1980 [1]. Patients with cirrhosis can develop acute renal failure, which is referred to as hepatorenal syndrome (HRS). The incidence and prevalence of HRS in patients with advanced liver disease have been reported to be approximately 7.6% and 13%, respectively [2]. HRS is characterized by marked renal arterial vasoconstriction with a consequent reduction in the renal plasma flow and the glomerular filtration rate. Terlipressin is an analog of vasopressin that is used in the treatment of patients with cirrhosis and gastroesophageal variceal bleeding and also used in treatment of patients with HRS [3]. Currently, the administration of a vasoconstrictor plus albumin is the most common approach in patients with HRS as this approach has been proven to be effective in the treatment of HRS among patients with cirrhosis and ascites [4,5]. Although terlipressin has an acceptable side effect profile when compared with the profile of vasopressin, there have been case reports on ischemic side effects associated with terlipressin administration, including skin ischemia [6,7], ventricular dysfunction [8], peripheral gangrene [9], ischemic necrosis [10,11], and acute myocardial infarction [12]. Here, we report a case of extensive peripheral cyanosis involving the fingers, toes, area around an umbilical hernia, and scrotum following terlipressin administration in a cirrhotic patient with HRS. The patient's condition rapidly improved on discontinuing the administration of the drug. To the best of our knowledge, this is the first report regarding terlipressin-induced peripheral cyanosis involving multiple sites. Our aim is to raise awareness among physicians regarding the adverse effects of terlipressin so that the condition can be detected and treated early.

Case Report

A 65-year-old man was admitted to our emergency department with worsening abdominal pain and epigastric pain for 1 day. He had medical history of liver cirrhosis classified as Child-Pugh class B, hypoalbuminemia, hypertension, a gastric ulcer, and insomnia. Additionally, he had a history of extensive alcohol consumption and smoking for over 10 years; however, he had stopped drinking alcohol and smoking after experiencing liver disease. At admission, he experienced dizziness and general weakness, but he was alert. His body temperature was 37.7°C, his blood pressure was 77/58 mmHg, his heart rate was 92 beats per minute, and his respiratory rate was 18 breaths per minute. His abdomen was soft and distended with shifting dullness, and a prominent umbilical hernia was noted.

Table 1. The initial laboratory data of the patient.

Parameter	Patient's value	Reference range
SrCr (mg/dL)	2.4	0.64–1.27
eGFR (mL/min/1.73 m ²)	28.9	–
BUN (mg/dL)	29.2	1–20
TP (g/dL)	8.3	6.1–7.9
Alb (g/dL)	2.2	3.5–4.8
T-Bil (mg/dL)	3.5	0.3–1.2
AST (IU/L)	114.0	5–41
ALT (IU/L)	44.0	5–40
ALP (IU/L)	98.0	32–91
Hb (g/dL)	10.2	13.5–17.5
WBC (×10 ⁹ /L)	2.0	4–10.8
RBC (×10 ¹² /L)	3.59	4.5–6.0
Plt (×10 ⁹ /L)	69.0	130–400
hs-CRP (mg/L)	17.6	0–10
PT (s)	13.3	8–12
INR	1.29	–
Na (mmol/L)	129	136–144
K (mmol/L)	4.2	3.6–5.2
NH ₃ (μg/dL)	83.0	5–70
Lactate (mmol/L)	5.8	0.5–2.2

SrCr – serum creatinine; eGFR – estimated glomerular filtration rate; BUN – blood urea nitrogen; TP – total protein; Alb – albumin; T-Bil – total bilirubin; AST – aspartate transaminase; ALT – alanine transaminase; ALP – alkaline phosphatase; Hb – hemoglobin; WBC – white blood cell; RBC – red blood cell; Plt – platelet; hs-CRP – high sensitivity C-reactive protein; PT – prothrombin time; INR – international normalized ratio; Na – sodium; K – potassium; NH₃ – ammonia.

Ascitic fluid analysis identified a deep yellow cloudy fluid. Cardiopulmonary examination findings were unremarkable. Blood and urine cultures were carried out and diagnostic paracentesis was performed. The initial laboratory findings are shown in Table 1.

The patient was admitted to the internal intensive care unit. On the second day, severe abdominal fullness and irritable mood were observed. Abdominal paracentesis was performed. Considering the development of spontaneous bacterial peritonitis, intravenous empiric, broad-spectrum antibiotics were administered immediately after peritoneal fluid collection. On the



Figure 1. On the third day of terlipressin therapy, peripheral cyanosis of the fingers, area around the umbilical hernia, and scrotum is observed.



Figure 2. On the fifth day after discontinuing terlipressin administration, improved peripheral cyanosis of the fingers, area around the umbilical hernia, and scrotum is observed.

following day, the blood and ascitic fluid cultures were negative. However, on the seventh day, oliguria with conscious confusion was noted. His urine output decreased to 60 mL over a period of 24 hours. Additionally, his serum creatinine level gradually increased to 4.0 mg/dL, the estimated glomerular filtration rate decreased to 16.1 mL/min/1.73 m², and the serum potassium level increased to 5.4 mmol/L. Moreover, his total serum bilirubin level increased greatly (4.1 mg/dL). His blood pressure was 88/51 mmHg. According to classical diagnostic criteria [13], a diagnosis of type-1 HRS was considered because his serum creatinine level almost doubled from baseline to the last assessment. The patient was not currently receiving any non-steroidal anti-inflammatory or other nephrotoxic drugs.

The patient received intravenous terlipressin (1 mg/5 mL/vial; 2 mg, 4 times a day) alone with human albumin (20%, 50 mL/bottle; 3 bottles a day). During the first 48 hours, terlipressin was administered at 2 mg every 6 hours, and thereafter, it was administered at 1 mg every 6 hours. On the second day of terlipressin administration, his urine output increased

to 750 mL and blood pressure increased to 128/88 mmHg. Unfortunately, on the third day of terlipressin administration, he developed cold extremities and peripheral cyanosis, resulting in purple discoloration of the affected sites, including the fingers, toes, area around the umbilical hernia, and scrotum (Figure 1). Intravenous administration of terlipressin was immediately discontinued. On the next day, the bluish skin showed some improvement, and on the fifth day after discontinuation, a complete recovery was noted (Figure 2).

To assess the relationship of terlipressin use with the patient's symptoms, his Naranjo probability algorithm score was calculated. A score of 6 was identified, suggesting a drug-induced reaction. This score was obtained because the symptoms appeared after the administration of the suspected drug and the symptoms improved after discontinuation of the suspected drug. Additionally, there were no alternative causes for the reaction, and the reaction has been conclusively reported previously. As there was a temporal relation between stopping terlipressin administration and regression of skin discoloration,

terlipressin-induced vasoconstriction was the most likely cause of his peripheral cyanosis [14].

Discussion

HRS is a severe complication of advanced liver cirrhosis in patients with ascites. If HRS is suspected, it should be treated as soon as possible [15]. The combination of a vasoconstrictor and albumin is considered as the pharmacological treatment of choice in the management of HRS. The vasoconstrictors used in the management of HRS include vasopressin analogs such as terlipressin, and alpha-adrenergic agonists such as noradrenaline and midodrine. Vasoconstrictors are administered to counteract splanchnic arterial vasodilation, which improves renal perfusion. Among these drugs, terlipressin is the most widely used agent. Many studies have shown that the combination of terlipressin and albumin can improve not only the renal function but also the short-term survival in patients with HRS [16–18].

It has been proposed that terlipressin should be intravenously administered at a dose of 1 mg every 4–6 hours, and if the serum creatinine level does not reduce by more than 25% after 2 days of treatment, the dose should be increased every 48 hours up to a maximum dose of 12 mg/day. Terlipressin administration should be discontinued after 2 weeks in non-responders. However, the dose of albumin in HRS treatment has not been well established. In general, albumin is used intravenously at a mean dose of 20–40 g/day until complete response (serum creatinine level <1.5 mg/dL).

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Terlipressin treatment can cause certain unwanted effects. Therefore, it is important to closely monitor the patient. In clinical trials, the most common side effects of terlipressin administration were paleness, increased blood pressure, peripheral ischemia, abdominal pain, nausea, diarrhea, and headache. A real-world observational study showed that terlipressin related adverse events are common [19]. The incidence of adverse events during terlipressin administration was 50.0%. Most of terlipressin related adverse events were mild or moderate, which can be resolved spontaneously without any intervention. As terlipressin acts mainly on the splanchnic vessels, the incidence of severe ischemic complications is lower with terlipressin than with vasopressin. However, it may cause serious complications such as myocardial infarction, intestinal ischemia, peripheral cyanosis, and skin necrosis. The rate of discontinuation of terlipressin administration due to side effects (mainly cardiovascular) has been reported to be approximately 20% [20].

Conclusions

In our patient case, the terlipressin-induced peripheral cyanosis involved multiple sites, including the fingers, toes, area around the umbilical hernia, and scrotum, and completely regressed after discontinuation of terlipressin administration. It is important to recognize the early signs of side effects and to discontinue administration of the suspected drugs immediately. Healthcare providers should report unusual adverse drug reactions associated with terlipressin use.

Conflict of interest

None declared.

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