

Secondary Scrotal Necrosis to Terlipressin Treatment in a Patient with Hepatorenal Syndrome

Hepatorenal Sendromlu Bir Hastada Terlipressin Tedavisine İkincil Skrotal Nekroz

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Abstract

Hepatorenal syndrome is a reversible acute renal impairment that occurs in patients with advanced liver cirrhosis or fulminant hepatic failure. Terlipressin is a synthetic long-acting analogue of vasopressin that is used in the treatment of hepatorenal syndrome. Ischemic adverse events of the treatment with terlipressin have been reported. We present a rare complication of terlipressin usage, ischemic skin necrosis of the scrotum, in a patient with advanced liver cirrhosis and hepatorenal syndrome.

Keywords: Glypressin, Hepatorenal Syndrome, Liver Cirrhosis, Vascular

Öz

Hepatorenal sendrom, ilerlemiş karaciğer sirozu veya fulminan karaciğer yetmezliği olan hastalarda ortaya çıkan, tersinir bir akut böbrek yetmezliğidir. Terlipressin, hepatorenal sendromun tedavisinde kullanılan sentetik uzun süre etkili bir vazopressin analogudur. Terlipressin ile tedavinin iskemik advers olayları bildirilmiştir. Karaciğer sirozu ve hepatorenal sendromlu bir hastada terlipressin kullanımının nadir görülen bir komplikasyonunu, skrotumun iskemik cilt nekrozunu sunuyoruz.

Anahtar Kelimeler: Glipressin, Hepatorenal Sendrom, Karaciğer Sirozu, Vasküler

Introduction

Hepatorenal syndrome (HRS) is a reversible acute renal impairment that occurs in patients with advanced liver cirrhosis or fulminant hepatic failure. The main treatment of HRS is liver transplantation. Vasoactive agent terlipressin is an arginine vasopressin analogue, which may be used in HRS and acute variceal bleeding. Terlipressin decreases portal venous pressure by inhibiting vasodilation of splanchnic vascular area that holds an important place at the pathogenesis of HRS (1,2). The reversal of renal function and increased urine output of the patients who used terlipressin has been reported in the literature (1-6).

Terlipressin may cause some common adverse effects such as arrhythmia, electrolyte imbalances, abdominal cramps, chest pain, nausea, headache, bradycardia, myocardial infarction, paleness, acral cyanosis, and diarrhoea (3).

Herein, we present a rare adverse effect of terlipressin in a patient with liver cirrhosis who developed ischemic skin necrosis of the scrotum after administration of intravenous terlipressin to treat HRS.

Case

A 67-year-old man presented with marked abdominal distension relevant to large volume ascites. The condition was secondary to hepatitis B virus cirrhosis and hepatocellular carcinoma. His medical history also included hypertension for the last 20 years and ischemic stroke for the last 12 years. He had cholecystectomy 20 years ago. At admission, the patient was taking zidovudine 300 mg, furosemide 40 mg, and spironolactone 100 mg once daily, and lactulose 20 ml every 12 hours. His Child-Turcotte-Pugh score was 12 (grade C) (2), and model for end-stage liver disease (MELD) score was 30 (7). He never smoked, but he was a social drinker in the past.

Laboratory test results were: hemoglobin (Hgb): 15.3 g/dL, leucocytes: 5.7 K/uL, platelets (PLT): 46 K/uL, prothrombin time (PT): 18 sec, international normalized ratio (INR) :1.6, total bilirubin:11 mg/dL, conjugated bilirubin:8.5 mg/dL, fasting glucose: 87 mg/dL, total protein: 6.6 g/dL, albumin 2.7 g/dL, creatinine: 2.75 mg/dL, sodium (Na): 139 mmol/L, and potassium (K): 3.9 mmol/L. Admission urinalysis showed the urine density: 1020, bilirubin: positive, protein, glucose, ketone and nitrite: negative, microscopic sediment: 2-3 leukocytes/mm³.

Abdominal paracentesis was performed for diagnostic and therapeutic reasons. Evaluation of the ascitic fluid sample signified transudative ascites with a serum-ascites albumin gradient (SAAG)>1.1 g/dL, and ruled out spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis was excluded via the cell count and culture of the ascitic fluid. Laboratory results showed the ascitic fluid protein concentration: 0.5 g/dL, ascitic fluid albumin

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concentration: 0.1 g/dL, white blood cell count (WBC): 120/mm³, polymorphonuclear leukocytes (PMNL): 42/mm³ and the fluid culture: negative. Ascitic drain was performed to alleviate the pain and respiratory symptoms of the patient. Based on the guidelines, 100 ml of 20% human albumin solution for every 2-3 L of drained ascitic fluid was administered concomitantly for the compensation of paracentesis.

Following the ascitic fluid drain, the bedside abdominal ultrasound showed nodular cirrhosis of a small sized liver with gross ascites and splenomegaly, and there was no evidence of renal parenchymal disease.

Dated by 22.01.2015, the endoscopic ultrasound (US) of the upper gastrointestinal tract revealed three columns of Grade 2 and 3 esophageal varices. There were no signs of acute bleeding.

From the 3rd to the 6th days of his hospital stay, the urine output of the patient declined to less than 30 ml/min and the serum creatinine level raised to 4.9 mg/dL. At that period of time, diuretics were withdrawn and 100 ml 20% human albumin was administered daily for 3 days.

The patient was consulted with the nephrology department. Despite the lack of specific diagnostic tests, diagnosis of HRS was made according to criteria defined by the International Ascites Club (6). Terlipressin by intravenous infusion was administered at a dose of 2 mg/2 h, in every 6 h. Intravenous albumin was maintained at its previous dose for the duration of therapy with terlipressin, as studies have suggested that albumin improves the beneficial effects of terlipressin on renal function (2-4,6). Both the renal and liver functions slightly improved. Within five days of concomitant treatment, a subsequent fall in serum creatinine level to 1.5 mg/dl and in serum total bilirubin level to 8 mg/dL together with an increase in the urine output were remarkable. During treatment, the patient was closely monitored for any adverse events, such as ischemic heart attack and stroke. Unfortunately, we observed ecchymotic-necrotic changes on the scrotum skin after 72 hours of terlipressin infusion (Fig 1). Doppler US was performed to evaluate the scrotal skin changes. Arterial and venous circulation in the major pelvic and scrotal arteries and veins demonstrated to be normal. There were no signs of thrombi or atherosclerotic plaques under suboptimal evaluation. Laboratory tests excluded infection. Radiological, laboratory and physical findings directed us to suspect from terlipressin-induced ischemic skin changes of the scrotum. Terlipressin dose was reduced by 50% on the 4th day of treatment and discontinued subsequently on day five. Dressings with hydrocolloid solutions together with local and systemic antibiotics had no benefit on the cutaneous lesions and the patient got worse.

Before the surgeons took a biopsy from the ecchymotic-necrotic skin lesions on the scrotum,



Figure 1. Ischemic skin necrosis of the scrotum after administration of terlipressin in a patient with hepatorenal

massive bleeding from the esophageal varices occurred. Application of endoscopic band ligation (date:04.02.2015; protocol no:19547811) and concomitant infusions of somatostatin and proton pump inhibitors could not control the bleeding. Two days later, the patient died of massive esophageal variceal bleeding.

Discussion

Terlipressin is a long-acting analogue and a prohormone of triglycyl-lysine-vasopressin (VP). Vasopressin type-1 receptors (V1 receptors) are found at smooth muscles, skin, blood vessels of splanchnic area, kidney and bladder (3-6, 8). Several studies have revealed that terlipressin is effective in controlling variceal bleeding and improves renal function in hepatorenal syndrome by decreasing renal vasoconstrictor system activity (1, 3-6, 8).

Terlipressin have multiple advantages in administration. It does not require continuous infusion or dose splitting as, the glycyl residues are cleaved from the prohormone by endothelial peptidases, allowing prolonged release of lysine-vasopressin after intravenous administration of terlipressin. This mechanism prolongs the half-life of terlipressin, enabling administration of undivided doses without the need for an infusion as with vasopressin (3,4). Terlipressin has lesser adverse effects compared to other vasopressin analogues. These adverse effects, such as arrhythmia, bradycardia, chest pain, electrolyte imbalances, abdominal cramps, nausea, diarrhea, headache, paleness, and acral cyanosis are usually mild (2,5). However, ischaemic events of the myocardium, and skin necrosis involving the extremities, scrotum, penis or abdomen are usually serious (2,4,5,9).

Terlipressin is not recommended in patients with a history of ischemic stroke as in our patient. Nonetheless, it was used in the dose as mentioned above with close monitoring. According to the literature, secondary ischemic side effects of terlipressin vary between 5% and 29% (2,4-6). These are myocardial infarction, ischemic colitis and skin necrosis (5). Ischemic skin necrosis has been reported on the extremities, abdominal skin, tongue,

scalp, breast, esophagus, and scrotum (8). Leading cause of the skin necrosis is the disturbed circulation of the skin.

In our case, scrotal skin necrosis with terlipressin was observed after 3 days of treatment and similar manifestations were reported previously in other cases (8-10).

These cases have involved the ischemic lesions of the scrotum, hips, abdominal region, trunk, and legs. Hypovolemia and concomitantly administered pressor drugs, obesity, ischemic diseases, venous insufficiency and spontaneous bacterial peritonitis were suggested to be predisposing factors of ischemic skin complications (9). Among these predisposing factors, hypovolemia at the present and the past ischemic stroke could be the possible predisposing factors in this case. Continuous intravenous infusion of terlipressin was also suggested to be one of the possible risk factors of ischemic adverse events (10). Our patient received 2 hours of terlipressin infusion at 6 hour intervals, and we could not predict if this was the possible risk factor of ischemic adverse event.

Unlike the other cases, ischemic skin necrosis stayed limited to scrotum only without affecting any other part of the body. It is considered that this case is one of the rare conditions to be reported.

In conclusion, ischemic skin necrosis is a rare side effect of terlipressin therapy. In our case, ischemic skin lesions were observed only on the scrotum. That is important in the differential diagnosis of scrotal pathologies. Although rare, ischemic skin necrosis on the scrotal region during the use of terlipressin especially in patients with hepatorenal syndrome should be kept in mind.

Informed Consent: Written informed consent was obtained from patient who participated in this case (20.01.2015).

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