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## Terlipressin-Induced Ischemic Skin Necrosis: A Rare Association

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Conflict of interest:** None declared

**Patient:** **Male, 65**  
**Final Diagnosis:** **Drug-induced skin necrosis**  
**Symptoms:** —  
**Medication:** —  
**Clinical Procedure:** **Skin graft**  
**Specialty:** **Surgery**

**Objective:** **Adverse events of drug therapy**





**Background:** Terlipressin is a synthetic vasopressin analogue that is used in the treatment of bleeding esophageal varices and hepatorenal syndrome in patients with cirrhosis. Serious ischemic adverse events, such as skin necrosis involving the extremities, scrotum, trunk, and abdominal skin, are rarely observed. In the literature to date, 20 cases that developed ischemic skin necrosis due to terlipressin usage have been reported.

**Case Report:** We report a patient with extensive skin necrosis on the infusion site of the right forearm and hand, which developed after the use terlipressin used to treat bleeding oesophageal varices in a 65-year-old man with cirrhosis.

**Conclusions:** Although rare, ischemic complications of terlipressin do occur.

**MeSH Keywords:** **Liver Cirrhosis • Lypressin • Skin Diseases, Vascular**

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## Background

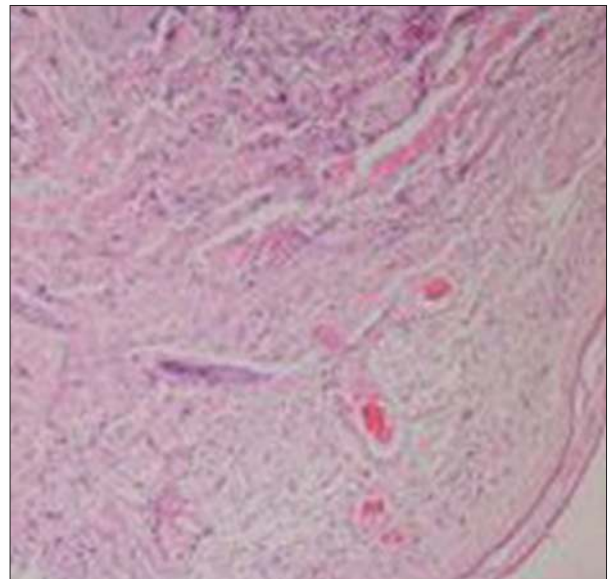
Terlipressin is a synthetic long-acting analogue of vasopressin, which is widely used in the treatment of cirrhotic patients with variceal bleeding and hepatorenal syndrome. It is a vasoconstrictor that acts preferentially on the splanchnic circulation, lowering portal venous pressure [1]. In the management of bleeding esophageal varices, terlipressin was shown to decrease mortality, reduce the failure rate of initial hemostasis, and reduce the number of emergency procedures to stop uncontrolled bleeding or rebleeding. The overall efficacy of terlipressin in controlling variceal bleeding is approximately 75–80%, and is especially effective when administered early [2]. The safety profile of terlipressin is better than vasopressin. However, vasoconstrictor effects on the systemic circulation result in ischemic complications in <5% of cases [3,4]. In the literature to date, 20 patients who developed ischemic skin necrosis due to terlipressin usage have been reported. Here, we report a patient with extensive skin necrosis on the infusion site of the right forearm and hand, which developed after the use terlipressin used to treat bleeding oesophageal varices in a 65-year-old man with cirrhosis.

## Case Report

A 65-year-old man presented with variceal hemorrhage secondary to non-alcoholic fatty liver disease (NAFLD) cirrhosis. His medical history included hypertension and ischemic heart disease. His body mass index (BMI) was 28 kg/m<sup>2</sup>. He had no bleeding episode and laboratory test results were: hemoglobin (Hgb): 10.3 g/dl, mean corpuscular volume (MCV): 86 fL, platelets (PLT): 110.000/mm<sup>3</sup>, prothrombin time (PT): 16-s international normalized ratio (INR): 1.4, alanine aminotransferase (ALT): 45 U/L, aspartate aminotransferase (AST): 65 U/L, gamma-glutamyl transferase (GGT): 87 IU/L, albumin: 2.8 g/dl, creatinine: 1.0 mg/dl, sodium (Na): 131 mmol/L, and potassium (K): 4.02 mmol/L. His model for end-stage liver disease (MELD) score on presentation was 10. Ultrasound (US) imaging showed hepatomegaly with Grade 2–3 hepatosteatosis and splenomegaly. There was no history of alcohol use. His viral serologic test results and test results for autoimmune hepatitis did not reveal any abnormality. The bleeding oesophageal varices were controlled with endoscopic banding and the addition of terlipressin and intravenous antibiotics. Terlipressin was used at a dose of 1 mg intravenously every 4 h. Following 2 days of treatment, the patient developed large areas of erythema, as well as swelling and bruising on the skin of the extensor side of the right forearm and hand but sparing the fingers (Figure 1). We attempted to diagnose the causes of the skin lesion by repeated blood culture, lesion and skin biopsy, and Doppler US. Cultures from the lesion and blood cultures were sterile. Doppler US demonstrated normal arterial



**Figure 1.** Large ischemic changes on the extensor side of right forearm and hand.



**Figure 2.** Cutaneous biopsy revealed vascular congestion in the upper dermis and non-specific inflammation extending from dermis into subcutaneous fatty tissue. There was no evidence of thrombi or vasculitic signs in the dermal vessels (hematoxylin and eosin  $\times 200$ ).

blood flow in the major arteries (ulnar, radial, and brachial). Cutaneous biopsy revealed non-specific inflammation extending from the dermis into the subcutaneous fatty tissue, and vascular congestion in the upper dermis. There was no evidence of thrombi or vasculitic signs in the dermal vessels (Figure 2). From these results and physical examination, we suspected a terlipressin-induced ischemic skin complication. The terlipressin injection was immediately discontinued and the wound on the right forearm was dressed with hydrocolloid solution. Despite cessation of terlipressin, his skin condition worsened, with development of extensive areas of necrosis. Finally, necrotic tissue was extracted and a skin graft was done.

## Discussion

Terlipressin is a prohormone of lysine-vasopressin (VP) (3 glycol residues and lysine-VP). Following intravenous administration, the glycol residues are cleaved from the prohormone by endothelial peptidases, allowing prolonged release of lysine-VP. This mechanism prolongs the half-life of terlipressin, enabling administration of undivided doses without the need for an infusion as with vasopressin [1]. Terlipressin administration, after 30 min, has been shown to significantly increase mean arterial pressure and systemic vascular resistance, while heart rate, cardiac output, hepatic venous portal pressure gradient, and portal venous blood flow decrease significantly [5,6]. It has been found to be superior to placebo in the control of variceal bleeding and to decrease renal vasoconstrictor system activity and improve renal function in patients with hepatorenal syndrome [1,3].

Terlipressin is the agent most frequently recommended for the control of acute bleeding. It is administered in a dose of 2 mg every 4 h for 2–5 days. After bleeding is controlled, it may be administered at a lower dose of 1 mg every 4 h for up to 5 days [7]. Adverse effects of terlipressin are usually mild and include skin pallor, headache, abdominal pain, bradycardia, hypertension and hyponatremia. It can exert vasoconstrictor effects on the systemic circulation; serious ischemic complications are rare and include myocardial infarction, ischemic colitis, and skin necrosis [8–10]. In the English literature to date, terlipressin-induced skin necrosis have been reported in 20 cases, located on the abdominal wall, thigh, leg, calves, fingers, toes, tongue, scalp, scrotum, breast, and esophagus [11–14].

Because our patient had ischemic heart disease, he was closely monitored for myocardial infarction. On the second day of the treatment, a red-purple color change was observed, covering the patient's right forearm. Despite the discontinuation of terlipressin treatment, the lesions progressed for 1 week. To the best of our knowledge, this is the first report of skin necrosis on the forearm due to terlipressin.

In all cases, including ours, skin manifestations evolved after 2–3 days of treatment, suggesting a dose-related effect. Potential predisposing factors of ischemic skin complications are hypovolemia, concomitantly administered pressor drugs, and patients with ischemic disease, obesity, venous insufficiency, or spontaneous bacterial peritonitis [12,15,16]. Some experts have suggested that continuous intravenous infusion of terlipressin was the possible risk factor of ischemic adverse events [17,18]. In our case, terlipressin was administered as an intravenous bolus and no other vasoactive drug was concomitantly administered. In the present case, history of atherosclerotic change of upper extremity vessels, hypovolemia, and overweight were possible risk factors for the peripheral gangrene and necrosis.

When we examined the cases of skin necrosis due to terlipressin, the reasons of liver failure were reported as alcoholic cirrhosis in 10 cases, obesity and NAFLD in 5 cases, metastatic carcinoma in 2 cases, viral hepatitis in 2 cases, and autoimmune hepatitis in 1 case. Therefore, we conclude that alcohol use should be considered as a potential risk factor for terlipressin-related skin necrosis.

The development of skin necrosis is related to the particular distribution of the target receptor of terlipressin – the vasopressin receptor type 1 (V1 receptor) – which is located in smooth muscles of the blood vessels, mainly in the area of the splanchnic circulation, kidney, myometrium, bladder, adipocytes, and skin circulation. Thus, the damaged areas in our case reinforce the probability of terlipressin as the cause [17].

## Conclusions

In conclusion, we report a patient with extensive skin necrosis in an unusual location, secondary to terlipressin therapy for management of variceal bleeding. Although rare, clinicians must bear in mind the possibility of ischemic complications caused by terlipressin. In addition to the obesity, NAFLD, and ischemic heart disease, it was important to think that alcohol use was a possible risk factor for progressive ischemic necrosis due to terlipressin.

## References:

1. Krag A, Borup T, Moller S, Bendtsen F: Efficacy and safety of terlipressin in cirrhotic patients with variceal bleeding or hepatorenal syndrome. *Adv Ther*, 2008; 25: 1105–40
2. Abraldes AJ, Dell' Era A, Bosch J: Medical management of variceal bleeding in patients with cirrhosis. *Can J Gastroenterol*, 2004; 18: 109–13
3. Ortega R, Gines P, Uriz J et al: Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, non-randomized study. *Hepatology*, 2002; 36: 941–48
4. Moreau R, Durand F, Poynard T et al: Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology*, 2002; 122: 923–30
5. Moller S, Hansen EF, Becker U et al: Central and systemic hemodynamic effects of Terlipressin in portal hypertensive patients. *Liver*, 2000; 20: 51–59
6. Krag A, Bendtsen F, Mortensen C et al: Effects of a single Terlipressin administration on cardiac function and perfusion in cirrhosis. *Eur J Gastroenterol Hepatol*, 2010; 22: 1085–92
7. Lee MY, Chu CS, Lee KT et al: Terlipressin-related acute myocardial infarction. *Kaohsiung J Med Sci*, 2004; 20: 604–8
8. Schmitt W, Wagner-Thiessen E, Lux G: Ischaemic colitis in a patient treated with Glypressin for bleeding oesophageal varices. *Hepatogastroenterology*, 1987; 34: 134–36

9. Lee HJ, Oh MJ. A case of peripheral gangrene and osteomyelitis secondary to terlipressin therapy in advanced liver disease. *Clin Mol Hepatol*, 2013; 19: 179–84
10. Fabrizi F, Dixit V, Martin P: Meta-analysis: terlipressin therapy for the hepatorenal syndrome. *Aliment Pharmacol Ther*, 2006; 24: 935–44
11. Mégarbané H, Barete S, Khosrotehrani K et al: Two Observations Raising Questions about Risk Factors of Cutaneous Necrosis Induced by Terlipressin (Glypressin®). *Dermatology*, 2009; 218: 334–37
12. Di Micoli A, Bracci E, Cappa FM et al: Terlipressin infusion induces ischemia of breast skin in a cirrhotic patient with hepatorenal syndrome. *Dig Liver Dis*, 2008; 40: 304–5
13. Donnellan F, Cullen G, Hegarty JE, McCormick PA: Ischaemic complications of Glypressin in liver disease: a case series. *Br J Clin Pharmacol*, 2007; 64: 550–52
14. Efthymakis K, Massacesi C, Milano A et al: Acute esophageal necrosis: possible association with terlipressin. *Endoscopy*, 2014; 46(Suppl.1): E279–80
15. Vaccaro F, Giorgi A, Riggio O et al: Is spontaneous bacterial peritonitis an inducer of vasopressin analogue side-effects? A case report. *Dig Liver Dis*, 2003; 35: 503–6
16. Yefet E, Gershovich M, Farber E, Soboh S: Extensive epidermal necrosis due to terlipressin. *Isr Med Assoc J*, 2011; 13: 180–81
17. Halimi C, Bonnard P, Bernard B et al: Effect of terlipressin (Glypressin) on hepatorenal syndrome in cirrhotic patients: results of a multicentre pilot study. *Eur J Gastroenterol Hepatol*, 2002; 14: 153–58
18. Oh JE, Ha JS, Cho DH et al: A case of ischemic skin necrosis after glypressin therapy in liver cirrhosis. *Korean J Gastroenterol*, 2008; 51(6): 381–84