



# Cutaneous Complications of Terlipressin

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## Abstract

Three cases of skin changes in cirrhotic patients treated with the vasoconstrictor agent terlipressin. We identified three patients who developed skin necrosis and determined any factors, which put them at an increased risk of doing so. Two patients developed extensive skin necrosis over the abdomen & chest wall and lower limbs. The third patient had developed extensive necrosis of both lower limbs and digital gangrene. With increasing clinical use of terlipressin and an increasing incidence of obesity and non-alcoholic fatty liver disease-related cirrhosis, the incidence of these serious complications is likely to rise. Earlier recognition and treatment may lead to improved outcome.

## Key Words

Terlipressin, Ischaemic Complication, Skin Necrosis

## Introduction

Terlipressin is a non-selective V1 vasopressin analogue. Compared with vasopressin and other analogues, it is known to have similar vasoconstricting potency but much less severe ischaemic complications (1,2,3). Terlipressin is a synthetic long-acting analogue of vasopressin, which is now 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. However, vasoconstrictor effects on the systemic circulation may result in ischaemic complications. Peripheral ischaemic complications in the fingers and toes are well described with vasoconstrictor medication. We report three patients with extensive skin necrosis in unusual areas in cirrhotic patients treated with terlipressin

## Case 1

A 47-year-old obese man; a diagnosed case of cryptogenic cirrhosis of liver decompensated with ascites, hepatorenal syndrome, hepatic encephalopathy was admitted with lower limb oedema, jaundice with a bilirubin of 5.2 mg/dl and renal impairment with a creatinine of

2.7 mg/dl. His platelets were 120000/cu mm, prothrombin time (PT) was 15.1 s (11.5-13.5 s) with an activated partial thromboplastin time (APTT) of 39.6 s (23-35 s). He was subsequently commenced on terlipressin at a dose 0.5 mg qds, and albumin for treatment of hepatorenal syndrome. Two days later he started to develop bullous haemorrhagic lesions, initially of the legs but later spreading to involve the feet and thighs (*Fig 1*) and subsequently lead to digital gangrene of the left second toe (*Fig 2*). There was no evidence of arterial insufficiency or underlying infection. The skin biopsy revealed epidermal necrosis, acute ulceration and haemorrhage, with fibrin thrombi in superficial dermal vessels. In the absence of other causative agents these lesions were attributed to treatment with terlipressin. Despite cessation of this agent, the patient's lower limbs lesions worsened with the development of extensive areas of necrosis and gross fluid exudation. This coincided with a progression in both liver and renal failure. He became profoundly acidotic and hypotensive and died 5 days after starting the vasopressor therapy.

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**Fig 1 & 2. Bullous Skin Lesions And Digital Gangrene Over The Left & Right Foot In Case 1**

### Case 2

A 53-year-old woman, with underlying cirrhosis secondary to non-alcoholic fatty liver disease (NAFLD) and morbidly obese with a body mass index (BMI) of 48kg m<sup>-2</sup>, presented with ascites and hepatorenal syndrome with a creatinine of 4.2 mg/dl. Her renal function returned to normal following treatment with terlipressin, and albumin supplementation. Her ascites was controlled with large volume paracentesis and diuretic therapy. After 5 days of terlipressin she developed extensive bruising and large exudative blistering of the skin of the abdominal wall and upper thighs (Fig 3). Despite withdrawal of the terlipressin, her skin condition worsened. The patient's liver function deteriorated with worsening of jaundice and encephalopathy and died 2 days later.

### Case 3

A 41-year-old man presented with variceal haemorrhage secondary to alcoholic liver disease. The bleeding oesophageal varices were controlled with endoscopic banding and the addition of terlipressin, and intravenous antibiotics. During this time his renal function deteriorated with a creatinine of 2.1 mg/dl. His platelets were 135000/cu mm. The PT was prolonged at 22 s (11.5-13.5 s), as was the APTT at 76 s (23-35 s). Terlipressin was used at a dose of 1 mg qds intravenously. Following 3 days of treatment, the patient developed large areas of



**Fig 3 & 4 . Bullous Lesions With Echymosis over the Abdominal Wall in Case 2 & over the Posterior Aspect of Legs in Case 3**

ecchymosis and blistering on the skin over the posterior aspect of the thighs and legs (figure 4). Punch biopsy of the lesions showed subepidermal bulla formation with no inflammation. Terlipressin was stopped and the lesions started improving after 2 weeks of stoppage of the drug and the patient was discharged

### Discussion

Since its introduction in the early 1990s, terlipressin has revolutionized management of liver disease with roles in the treatment of variceal haemorrhage and hepatorenal syndrome (1,2,3,4). Terlipressin has proven to be safe, with a lower incidence of side-effects compared with vasopressin and other synthetic analogues. Although terlipressin is selective for the splanchnic circulation, it can exert vasoconstrictor effects on the systemic circulation. Undesirable effects are usually mild and include headache, paleness, abdominal pain and bradycardia. More serious complications are uncommon, but cases of skin necrosis (2,3), ischaemic colitis (5, 6), myocardial infarction (7) have been reported. We believe that the skin lesion seen in our three patients occurred as a result of terlipressin therapy. There is evidence for a causal relationship between terlipressin and the observed skin necrosis. The majority of cases related to skin necrosis affecting the extremities, but there are also a small number of cases of foreskin and scrotal necrosis in

males. Skin necrosis in atypical areas in obese or severely oedematous individuals has not been reported to date. Unfortunately, two out of the three patients described in this case series died as a result of multiorgan failure shortly (<72 h) after discontinuing terlipressin. This may explain why no improvement in the skin necrosis was observed on discontinuation of the drug. The affected areas in our three patients were atypical. Ischaemic complications as a result of vasoconstrictor medication usually affect peripheral areas such as the digits of the hands and feet. It is possible that the venous insufficiency and obesity in two of our patients, and marked anemia due to variceal bleed leading to decreased tissue perfusion, in one of our patients put them at increased risk.

We propose that both obesity, oedema, and marked anemia due to variceal bleed, led to stretching of the skin of the abdomen and lower limbs, increasing the surface area for the microvascular blood supply, thereby lowering tissue oxygen levels. We postulate that the presence of low tissue oxygen levels in combination with the use of a vasoconstrictor agent led to development of ischaemic complications. These cases suggest that extra vigilance is warranted in administering terlipressin to patients with cirrhosis of liver and clinicians should be aware of these potential complications, so that terlipressin is stopped right at the onset of such skin lesions to prevent further complications, as eyes do not see what the mind does not know.

## Conclusions

With increasing clinical use of terlipressin and an increasing incidence of obesity and non-alcoholic fatty liver disease-related cirrhosis, the incidence of these serious complications is likely to rise. Earlier recognition and treatment may lead to improved outcome. So the clinicians should be aware of ischaemic complications of terlipressin and should observe the patients for these complications, so that the drug is stopped once the patients develop such lesions.

## References

1. Vaccaro F, Giorgi A, Riggio O, De Santis A, Laviano A, Rossi-Fanelli F. Is spontaneous bacterial peritonitis an inducer of vasopressin analogue side effects? A case report. *Dig Liver Dis* 2003; 35:503-06.
2. 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.
3. Lee JS, Lee HS, Jung SW, *et al.* [A case of peripherals ischemic complication after terlipressin therapy]. *Korean J Gastroenterol* 2006; 47: 454-57
4. Gines P, Torre A, Terra C, Guevara M. Review article: pharmacological treatment of hepatorenal syndrome. *Aliment Pharmacol Ther* 2004; 20 (Suppl. 3): 57-62
5. Willems MG, Schoenemann J, Rey C, Schafer H, Lindecken KD. Ischaemia of the cecum caused by glycyllpressin. *Leber Magen Darm* 1985; 15: 165-68.
6. Schatt W, Wagner-Thiessen E, Lux G. Ischaemic colitis in a patient treated with Glypressin for bleeding oesophageal varices. *Hepatogastroenterology* 1987; 34: 134-36.
7. Lee MY, Chu CS, Lee KT, *et al.* Terlipressin-related acute myocardial infarction. *Kaohsiung J Med Sci* 2004; 20: 604-08.