



Terlipressin-Induced Irreversible Severe Skin Necrosis: A Dreadful Complication

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Abstract

Terlipressin (triglycyl lysine vasopressin), a synthetic analogue of vasopressin, has been employed in the last years for the treatment of upper digestive bleeding from esophagogastric varices and for hepatorenal syndrome. Several adverse effects have been reported, all reversible after dose reduction or drug interruption. The authors report two rare cases of irreversible severe skin necrosis induced by terlipressin infusion.

Keywords: Terlipressin; Portal hypertension; Digestive bleeding; Hepatorenal syndrome

Introduction

Esophageal variceal bleeding (EVBEVB) occurs in 10–20% of cirrhotic patients per year and each bleeding episode is associated with a 20 to 50 per cent in-hospital mortality [1,2]. The recommended treatment includes vasoactive drugs as Terlipressin (triglycyl lysine vasopressin) as adjuvant to endoscopic variceal band ligation (EVBL) [1-3]. Terlipressin has a different bioavailability profile from vasopressin, enabling it to be given as intermittent intravenous injections, with no effect on plasminogen activator and it is believed to have an intrinsic vasoconstrictor effect. In clinical trials it showed to induce a lower incidence of severe adverse reactions [4,5].

It has also been suggested that the use of terlipressin combined with intravenous albumin infusion may improve renal function in patients with cirrhosis and type 1 hepatorenal syndrome [6,7] (HRS). In spite of its benefits, adverse effects related to its vasoconstrictive properties have been reported. Although rare, terlipressin-related ischemic adverse effects acute ST-segment elevation myocardial infarction [8], severe lactic acidosis [9], extremities ischemia and gangrene [10] had been reported. We report two patients with severe lower limb skin necrosis not reversible even after terlipressin withdrawal.

Case Presentation

Case 1

A 47 year old man was admitted in the ICU with upper digestive bleeding due to gastric varices. He had been submitted to a Warren procedure sixteen years before for the treatment of portal hypertension due to hepatosplenic mansonic schistosomiasis. Terlipressin 1 mg every 4 hours was administered and an upper digestive endoscopy with cianoacrilate injection was performed. 24 hours later the patient developed skin blisters on the legs with progression to severe skin necrosis even after terlipressin suspension (Figure 1). Resection of the necrotic area and a skin graft were performed. The patient presented a good outcome and was discharged from hospital on the 48th day.

Case 2

A 68 year old man was admitted in the ICU with liver insufficiency with ascites, hepatic encephalopathy and hepatorenal syndrome after a right extended hepatectomy for colorectal metastasis. Terlipressin 1 mg every 6 hours and albumin were prescribed. 48 hrs later the patient presented severe skin necrosis of the legs and scrotum irreversible even after terlipressin suspension (Figure 2). The patient died due to multiple organ failure on the 38th postoperative day.

Discussion

Terlipressin is a prohormone (lysine-vasopressin) that after intravenous administration is cleaved by endothelial peptidases, allowing prolonged release of vasopressin. Vasopressin is a potent splanchnic vasoconstrictor but its use was abandoned many years ago in most countries because of its severe vascular side effects. Terlipressin, a vasopressin analogue, has similar effects reducing

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Figure 1: Pictures showing skin lesions evolving to necrosis (Patient 1).



Figure 2: Pictures showing skin necrosis of right knee and scrotum (Patient 2).

hepatic venous pressure gradient, variceal pressure and azygos blood flow and, due to its hemodynamic effects, have been used in the therapy of variceal hemorrhage [11,12].

Despite its excellent vasopressive effects, vasopressin analogues may potentially impair macro-hemodynamics, oxygen transport and microvascular blood flow. Terlipressin can induce ischemic complications, especially in patients with severe hypovolemic shock [13], and it is not indicated in patients with cardiovascular disease (arterial disease with severe obstruction, cardiac insufficiency, arrhythmias, and hypertension).

A meta-analysis showed efficacy and safety with the use of terlipressin in the treatment of hepatorenal syndrome [14]. The most frequent adverse effects reported were abdominal pain, arrhythmias and skin lesions, all of them reversible after dose reduction. Recently, cases reported describe ischemic complications of various parts of the body, such as hips, abdominal region, trunk, legs and scrotal region [15-19]. Nevertheless, the complications were reversible after terlipressin suspension. The terlipressin dosage administered to our patients was those recommended on the world's literature. Our patients presented irreversible skin lesions even after terlipressin suspension.

We believe that due to its bioavailability profile, terlipressin is slowly cleaved by endothelial peptidases to vasopressin [20], being possible that its vasoconstrictive action persists even after its interruption and that these prolonged action combined with a possible direct vasoconstrictive property could be responsible for the severe skin necrosis observed in our patients. Recent studies have suggested that terlipressin may also be administered as a low-dose continuous infusion (1.3-2.6 µg/kg) in the early course of distributive shock [21] with near the same hemodynamic effects [22,23].

Our data emphasizes the need of randomized trials for the establishment of the optimal terlipressin dosage, administration regimen and the occurrence of unwanted side-effects.

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