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CASE REPORT

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The "dark" side of terlipressin: a case report of ischemic skin necrosis and review of literature

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Abstract

Background Terlipressin is a commonly used drug in cirrhotic patients with acute variceal bleed (AVB) due to its vasoconstrictor effects. Ischemic complications are uncommon adverse events associated with worse outcomes.

Case presentation We present a case of alcohol-related cirrhosis, who was started on terlipressin for AVB. However, he developed bilateral lower limb gangrene with ischemic skin necrosis and ultimately succumbed to death.

Conclusion Although ischemic adverse events are uncommon with terlipressin, it is important to be aware of these complications as they may be severe and potentially life threatening.

Keywords Vasoconstrictors, Variceal bleed, Ischemic necrosis, Gangrene, Cirrhosis

Background

Terlipressin is widely used in the treatment of bleeding esophageal varices in patients with cirrhosis. It is found to decrease the mortality by reducing splanchnic blood flow and portal pressures and the need for emergency procedures required to stop rebleeding [1]. Ischemic adverse events are uncommonly observed with terlipressin of which cutaneous complications are among the rarest [2]. It is important to be aware of such uncommon events to facilitate early recognition and prompt withdrawal of terlipressin. Herein, we report a case of bilateral lower limb gangrene with ischemic skin necrosis in a patient of acute on chronic liver failure who was started on terlipressin for acute variceal hemorrhage.

Case report

A 45-year-old gentleman previously diagnosed with liver cirrhosis presented to the emergency with hematemesis, melena, and altered sensorium for 1 day. He had a history of significant alcohol consumption (60–80 g/day for last 20 years) but no tobacco or other substance abuse. There was no history of ischemic heart disease, peripheral vascular disease, or metabolic comorbidities including diabetes mellitus, hypertension, or obesity in the patient or his family members. On examination, he was disoriented, pale, and icteric with free fluid per abdomen as evidenced by shifting dullness. Patient was shifted to the intensive care unit and was intubated in view of poor sensorium. Intravenous ceftriaxone (1 g intravenously twice a day), terlipressin (intravenous boluses of 2-mg stat followed by 1 mg every 4 h), and other supportive management were started. Investigations revealed anemia (hemoglobin: 4.8 g/dL) with thrombocytopenia (92×10^3/μL) and leukocytosis (2×10^3/μL) with deranged liver (bilirubin: 3.8 mg/dL, *AST*: 384 IU/L, *ALT*: 141 IU/L), coagulation (*INR*: 1.7), and renal function parameters (blood urea nitrogen: 59.7 mg/dL, creatinine: 1.5 mg/

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dL). After stabilization, upper gastrointestinal endoscopy was performed which revealed large, high-risk esophageal varices with white nipple sign, and endoscopic variceal ligation was done. During the first 36 h of admission, he was also transfused with 3 units of packed red blood cells, and the hemoglobin was built up to 8.1 g/dL. On the 3rd day of admission, he developed cyanosis of bilateral lower limbs with absent peripheral pulses which progressed rapidly to bluish-black discoloration up to the knees and skin necrosis over left medial ankle (Fig. 1). Arterial Doppler corroborated the absence of flow in popliteal artery and its branches. Vasculitis work-up including ANA, ANCA, and complement levels was non-contributory. Terlipressin was stopped immediately. However, the patient continued to deteriorate with worsening sepsis, rise in total leukocyte counts, and development of new-onset shock. Despite upgradation of antibiotics and optimization of management, he had a rapidly downhill course and expired on day 5.

Discussion

Acute variceal bleed (AVB) is a potentially life-threatening complication of cirrhosis. Mortality has decreased substantially over the last three decades due to advancements in medical and endoscopic therapies. Current guidelines advocate combined endoscopic and pharmacological therapy in patients with AVB due to improved outcomes as compared to either modality alone [3]. Pharmacotherapy in AVB includes vasoconstrictors like terlipressin, somatostatin, and octreotide. Where available, terlipressin is usually the preferred vasoconstrictor as it has been shown to have a survival benefit [3]. It acts on V1 receptors in vascular smooth muscle cells leading to splanchnic vasoconstriction and reduction of portal venous pressures. Apart from AVB, terlipressin is also used in the management of hepatorenal syndrome (HRS) in cirrhosis and has been recently approved by the US FDA based on the phase 3 CONFIRM trial [4].

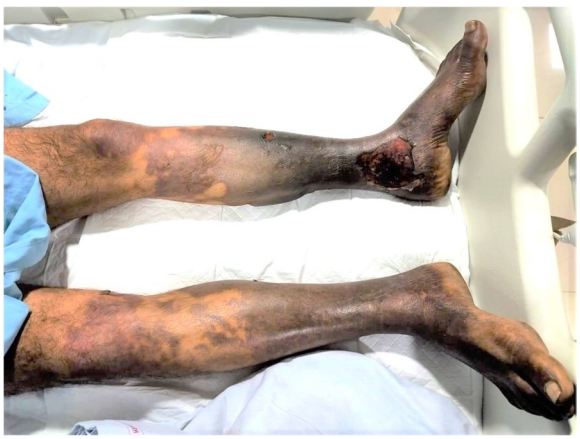

Fig. 1 Photograph depicting bilateral lower limb gangrenous changes with involvement up to the knee and skin necrosis over left ankle

Adverse events with terlipressin are infrequent. The most concerning adverse effects are related to respiratory failure, myocardial ischemia, arrhythmias, bradycardia, and fluid overload. Other commonly reported adverse events include abdominal pain, nausea, and dyspnea [4]. Ischemic complications with terlipressin are uncommon and were seen in 4.5% of patients in the phase 3 CONFIRM trial. These complications may range from intestinal ischemia and myocardial ischemia to peripheral gangrene. Cutaneous complications are rare and may include bulla, cyanosis, necrosis, and purpura. The exact incidence of ischemic skin necrosis and gangrene following terlipressin is difficult to estimate because of the rarity of the event. In a recently published prospective cohort study on the safety and efficacy of terlipressin, ischemic skin necrosis was documented in only one patient (0.9%) [5]. As such, fewer than 40 cases have been reported in the literature (Table 1), and it commonly involves legs followed by abdomen, scrotum, upper extremities, and hands. It is more common in patients with high MELD scores and those with underlying comorbidities like diabetes, hypertension, obesity, or cardiovascular disease [2, 6]. Our patient had a MELD score of 35 but did not have other comorbidities or risk factors for peripheral vascular disease.

It should be noted that our patient received bolus doses of terlipressin (2-mg stat followed by 1 mg 4 hourly) as is the usual practice in AVB [3]. In HRS, use of terlipressin as a continuous infusion instead of boluses has been shown to be equally effective with significantly less adverse effects and a lower cumulative dose [32]. However, data on the use of terlipressin as infusion for management of patients with AVB is virtually non-existent. Furthermore, ischemic complications including skin necrosis have also been reported with the use of continuous infusion of terlipressin in HRS [2, 6].

Development of ischemic complications with terlipressin is associated with increased morbidity and mortality, and there is no specific treatment to revert it. Terlipressin should be stopped immediately, and some cases may resolve with supportive care. Sildenafil has also been tried anecdotally with mixed results [2]. Therefore, patients receiving terlipressin should be closely watched out for terlipressin-induced ischemic events.

Table 1 Case reports until date of terlipressin-induced ischemic events

S. no	Authors	Age	Sex	Etiology	Risk factors	Indication	Dose	MELD	Outcome
1	Iglesias Julian et al. (2017) [7]	84	F	HCV	HTN, CRF	Variceal bleed	Bolus	28	Survived
2	Sarma et al. (2017) [8]	65	M	Ethanol	Diabetes	Variceal bleed	Bolus	-	Died
3	Ozel Coskun et al. (2014) [9]	65	M	NASH	Obesity/ischemic heart disease/HTN	Variceal bleed	Bolus	10	Survived
4	Sundriyal et al. (2013) [10]	47	M	Ethanol	NA	Variceal bleed	Bolus	-	-
5	Yefet et al. (2011) [11]	66	M	Ethanol	Obesity, ischemic heart disease, diabetes	Variceal bleed	Bolus	-	Died
6	Bañuelos Ramírez et al. (2017) [12]	51	F	Ethanol	Chronic kidney disease	Variceal bleed	Bolus	-	Survived
7	Elzouki et al. (2010) [13]	52	M	Cryptogenic	Diabetes, hypothyroidism	Variceal bleed	Bolus	12	Survived
8	Kumar N. et al. (2020) [14]	57	F	Ethanol		Variceal bleed	Bolus	-	Survived
9	Chandail VS et al. (2011) [15]	47 53 41	M F M	1. Cryptogenic 2. NASH 3. Ethanol	Obesity Obesity -	Hepatorenal syndrome Hepatorenal syndrome Variceal bleed	Bolus - Bolus		Died Died Survived
10	Donnellan et al. (2007) [16]	47 53 56	M F M	1. AIH 2. NASH 3. Ethanol	Venous insufficiency - -	Hepatorenal syndrome Hepatorenal syndrome Variceal bleed	Bolus + octreotide	24 23 9	Died Died Died
11	Simões Macedo S et al. (2019) [17]	71	M	NASH	-	Hepatorenal syndrome + variceal bleed	Bolus	-	Died
12	Cleva R. D. et al. (2016) [18]	47 68	M M	Ethanol	- -	Variceal bleed Hepatorenal syndrome	Bolus Bolus	- -	Survived Died
13	Chiang et al. (2019) [19]	65	M	Ethanol	HTN	Hepatorenal syndrome	Bolus	28	Survived
14	Herrera et al. (2015) [20]	55	M	Ethanol	ICH	Hepatorenal syndrome	Bolus	29	Died
15	Lee and Oh (2013) [21]	71	M	Ethanol + chronic hepatitis C	Prior pulmonary TB	Hepatorenal syndrome	Bolus	25	Survived
16	Taşliyurt et al. (2012) [22]	79 65	M M	1. Ethanol 2. Hepatitis B	-	Hepatorenal syndrome	Bolus	-	Died
17	Sahu et al. (2010) [23]	50	M	Ethanol	Diabetes	Hepatorenal syndrome	Bolus	-	Died
18	Posada et al. (2009) [24]	39	M	Ethanol	-	Hepatorenal syndrome	Bolus	-	Died
19	Mégarbané et al. (2009) [25]	68 74	M M	1. Ethanol/HCC 2. Adenocarcinoma	Diabetes, ischemic heart disease, dyslipidemia	Hepatorenal syndrome Pseudo-hepatorenal syndrome	Bolus Infusion	- -	Died Died
20	Di Micoli et al. (2008) [26]	65	F	HCC, hepatitis C	Hypothyroidism	Hepatorenal syndrome	Bolus + infusion	15	Survived
21									
22	Lee et al. (2006) [27]	41	M	Etiology	-	Hepatorenal syndrome	Bolus	30	-
23	Vaccaro et al. (2003) [28]	73	M	HCV	-	Hepatorenal syndrome	Bolus	28	Died
24	Karakus V. et al. (2019) [29]	67	M	Ethanol	HTN	Hepatorenal syndrome	Bolus	30	Died
25	Ahmed R. et al. (2018) [30]	50	F	Ethanol	HTN	Hepatorenal syndrome	Bolus	36	Died
26	Jain G. et al. (2021) [31]	54	M	Cryptogenic		Hepatorenal syndrome	Bolus	-	-
27	Our patient	45	M	Ethanol	-	Variceal bleed	Bolus	-	Died

Conclusion

Terlipressin is the most enthusiastically used drug in clinical practice in patients with AVB or HRS. However, it is uncommonly associated with ischemic complications that can prove detrimental. Hence, it is necessary to be in knowledge of such adverse events to facilitate early recognition and prompt withdrawal of terlipressin.

Abbreviations

AST	Aspartate transaminase
ALT	Alanine transaminase
ANA	Antinuclear antibody
ANCA	Anti-neutrophilic cytoplasmic antibody
AVB	Acute variceal bleed
HRS	Hepatorenal syndrome
US FDA	United States Food and Drug Administration
MELD	Model for end-stage liver disease

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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