Case Report

Terlipressin-induced Peripheral Ischemic Gangrene in a Diabetic Patient

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Abstract

Terlipressin is used commonly in the management of hepatorenal syndrome and acute variceal bleeding. Like its parent compound vasopressin, it is also notorious for its ischemic complications. Terlipressin-induced ischemic complications can virtually affect any part of the body, but the incidence of serious complications is less than its parent compound vasopressin. Here, we report a case of terlipressin-induced peripheral ischemic gangrene in a diabetic male, which ultimately led to death of the patient.

Keywords: Gangrene, hepatorenal syndrome, ischemic complication, terlipressin, variceal bleeding

Introduction

Acute variceal bleed and hepatorenal syndrome are the two important causes of morbidity and mortality in patients with cirrhosis. Acute bleeding esophageal varices is associated with 10%–50% mortality per episode.[1,2] Treatment options are pharmacotherapy (splanchnic vasoconstrictors, antibiotics), endoscopic therapy (ligation, sclerotherapy), other salvage procedures (balloon tamponade, transjugular intrahepatic portosystemic shunt, and balloon occluded transvenous retrograde obliteration), and surgical therapies such as distal splenorenal shunt, angiectomy, and liver transplantation. Among pharmacotherapeutic options are vasopressin and its analog (terlipressin) and somatostatin and its analogs (vapreotide and octreotide).[3] Pharmacotherapeutic interventions need comparatively less expertise than endoscopic procedures, but controversy exists regarding their risk–benefit ratio.[1] Vasopressin is the most potent splanchnic vasoconstrictor, but increased incidence of ischemic side effects limits its use. Terlipressin is a vasopressin analog with longer duration of action with fewer ischemic complications.[4] Vasoactive therapy is associated with significantly lower risk of acute all-cause mortality, transfusion requirements, improved control of bleeding and shorter hospital stay.[1] Although side effect profile of terlipressin is more favorable, compared to parent compound vasopressin, yet few cases are reported regarding ischemic complications of terlipressin therapy.[5-11]

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Ischemia leading to gangrene is a relatively rare adverse effect of terlipressin. Only few cases are reported till now. Here, we report a case of terlipressin-induced peripheral gangrene in a 65-year-old male patient with acute variceal bleed.

Case Report

A 65-year-old male diabetic (fasting blood sugar 166 mg/dl, postprandial blood sugar 240 mg/dl, HbA1c 8.1%) patient presented in emergency with complaints of hematemesis and melena for the past 24 h. He had been a chronic alcoholic consuming around 100 g of alcohol per day for the last 35 years. On evaluation, he was found to have hepatomegaly. His hemogram showed anemia (8.9 g/dl), thrombocytopenia (platelet count 0.4 lac/mm^3) with evidence of coagulopathy (prothrombin time index 48%). Ultrasound abdomen showed altered echotexture of liver with features of portal hypertension. On the basis of clinical, biochemical, and radiological imaging, provisional diagnosis of chronic liver disease with upper gastrointestinal (GI) bleed (variceal) was made and managed with blood transfusion, antibiotics,

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and splanchnic vasoconstrictor (injection terlipressin 1 mg 6 hourly). After initial stabilization, the patient underwent upper GI endoscopy which showed large esophageal varices, for which endoscopic variceal ligation was done. After 2 days of therapy, he developed blackening of bilateral upper and lower limbs (UL and LL) which was more prominent in distal parts [Figures 1-3]. This blackening evolved rapidly into large necrotizing areas with fluid exudation. On examination, his distal arterial pulses were palpable. Color Doppler study showed normal color flow and spectral waveform in all major arteries of bilateral UL and LL. X-ray of both bilateral UL and LL showed normal study.

Immediately, terlipressin was thought to be the culprit drug for this complication and was discontinued. After that, the proximal progression of discoloration stopped. Meanwhile, the patient was screened for markers of autoimmunity in the form of antinuclear antibody and antineutrophil cytoplasm antibody which were found to be negative.

He was given symptomatic treatment in the form of vigorous dressing, antibiotics, and intravenous fluids. He was offered amputation of bilateral toes and fingers to prevent further progression of the disease and resultant sepsis. However, the patient refused for an amputation and he went against medical advice. After 15 days, he died of sepsis at his home.

On causality assessment, by both WHO-UMC[12] and Naranjo scale,[13] terlipressin was found to be of probable category by both the classification systems while other concomitant medications were found to be of unlikely causality. Severity was assessed by modified Hartwig and Siegel Scale,[14] and it was found to be of severe category. Seriousness was assessed by US-Food and Drug Administration criteria[15] and it was a serious event. Preventability of the adverse drug reaction (ADR) was assessed by Schumock and Thronton's scale.[16] Moreover, this ADR was found to be of definitely not preventable category. Predictability analysis was done by predictability scale by Imbs *et al*.,[17] and it was found to be of definitely not predictable (Category C).

Discussion

Ischemic complications are relatively rare adverse effects of terlipressin therapy. In our case, the patient developed peripheral gangrene and succumbed to it. The spectrum of ischemic complication ranges from peripheral gangrene, myocardial ischemia, and ischemia of bowel, and the spectrum of ischemic complications practically involved every organ extending from scalp ischemia to ischemic complications of the scrotum.[5-11,18-21] Most cases were managed conservatively with stopping of terlipressin.[5-11,18-21] In two cases, sildenafil was tried as an intervention and one case recorded significant improvement and recovered completely at 1 month, while other case developed decreased urine output and alprostadil and sildenafil had to be withdrawn. Although amputation had to be done on medical grounds, this patient also recovered.[5,6] V1 receptor-mediated vasoconstriction and superimposed

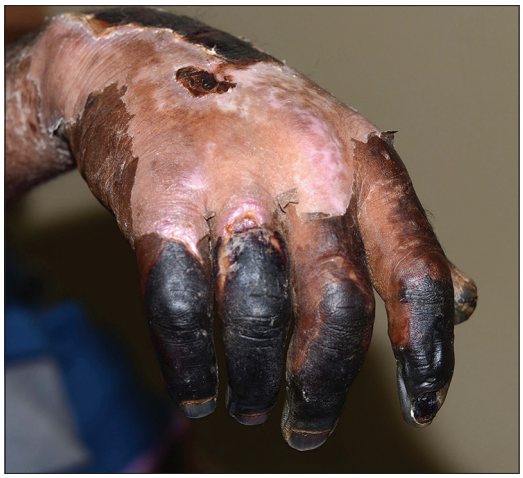

Figure 1: After 2 days of therapy, blackening of the upper limb

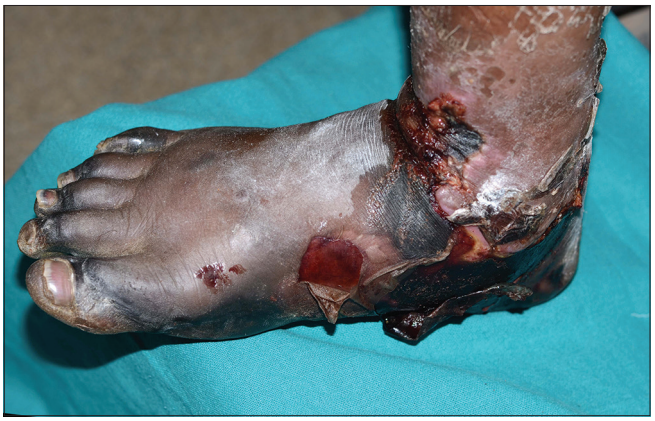

Figure 2: After 2 days of therapy, blackening of the lower limb

Figure 3: After 2 days of therapy, blackening of the lower and upper limbs

V2 receptor-mediated Von Will brand factor release from endothelial cells, together are implicated in the pathogenesis of ischemic complications.[22-24] Role of pharmacogenomics in vasopressin-induced ischemic complications was evaluated by Anantasit *et al*. and a significant association was found between serious adverse effects of vasopressin and

single-nucleotide polymorphism of rs28418396, implicating a role of pharmacogenomics in the prediction of ischemic complications.[23] This area needs further study. We report this rare adverse effect of terlipressin so that physicians will be aware of these dreaded adverse effects of terlipressin as timely detection and stopping of terlipressin at the earliest sign of ischemia can be lifesaving.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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