10.4414/cvm.2022.02222 | 2023;26(1):20–23 | Cardiovasc Med
Case report | Peer reviewed article

A synthetic analogue of vasopressin

Relapsing terlipressin-induced acute pulmonary oedema in a patient with hepatorenal syndrome

Baudouin Bourlond[a], Jean-Michel Dogné[b], Luis Urbano[a], Oscar Marchetti[a]
[a] Department of Medicine, Ensemble Hospitalier de la Côte (EHC), Morges, Switzerland; [b] Department of Pharmacy, University of Namur, Belgium

Summary

Terlipressin is a synthetic analogue of vasopressin recommended as a vasoactive drug with relative specificity for the splanchnic circulation in patients with portal hypertension and bleeding oesophageal varices or hepatorenal syndrome. We report a relapsing terlipressin-induced acute pulmonary oedema in a 59 year-old man with Child B9 alcoholic liver cirrhosis.

Introduction

Terlipressin is a synthetic vasopressin analogue with relative specificity for the splanchnic circulation, resulting in vasoconstriction aimed at reducing venous portal pressure in patients with bleeding esophageal varices or hepatorenal syndrome. Terlipressin has a longer half-life than vasopressin and its use is associated with fewer ischaemic complications [1].

Although the vasoconstrictive action of terlipressin on the systemic arterial circulation may result in arterial hypertension and myocardial ischaemia, cardiac adverse events are rarely reported despite its frequent use in patients at high risk for cardiovascular events [2–6]. We report a case of relapsing acute pulmonary oedema secondary to a hypertensive crisis induced by terlipressin infusion in the context of left ventricular hypertrophy with acute diastolic dysfunction.

Case description

We report the case of a 59-year-old man who was hospitalised for a decline of his general clinical condition with repeated falls. The patient was known to have peripheral artery occlusive disease, hypothyroidism, heavy alcohol consumption (20 U/day) and active tobacco use, without other cardiovascular risk factors.

Abdominal echography showed hepatosplenomegaly, liver steatosis and moderate ascites.

On admission, body temperature was 36.2 °C, blood pressure 137/86 mm Hg, heart rate 95/min and oxygen saturation 96% (SpO_2) while breathing ambient air. Cardiopulmonary auscultation was normal. The patient was icteric and had hepatosplenomegaly.

Laboratory findings were: aspartate aminotransferase (AST) 63 U/l (reference range 13–40), alanine aminotransferase (ALT) 125 U/l (7–40), gamma-glutamyl transpeptidase 789 U/ (<73), alkaline phosphatase 349 U/l (46–116), total bilirubin 86 µmol/l (<21), albumin 25 g/l (37–51), haemoglobin 141 g/l (135–175), platelets 281 G/l (150–450), international normalised ratio (INR) 1.3. C-reactive protein (CRP) 130 mg/l (0–10), leucocytes 24.7 G/l (4–10) with neutrophils 21.53 G/l (1.40–8.00), eosinophils 0.31 G/l (<0.70), basophils 0.08 G/l (<0.2), monocytes 1.06 G/l (0.16–0.95), lymphocytes 1.67 G/l (1.50–4.00), creatinine 62 mcmol/l (55–96) for an estimated glomerular filtration rate (eGFR) 103 ml/min.

Abdominal echography showed hepatosplenomegaly, liver steatosis and moderate ascites. Signs of portal hypertension were found, without portal vein thrombosis.

Based on these clinical, laboratory and radiological findings, a diagnosis of Child B9 liver cirrhosis with acute alcoholic hepatitis and portal hypertension was made.

Intravenous vancomycin treatment was started on day 2 for Enterococcus faecium urinary infection.

During the hospital stay (day 14 after admission), voluminous ascites developed, re-

Published under the copyright license "Attribution – Non-Commercial – NoDerivatives 4.0". No commercial reuse without permission. See: http://emh.ch/en/services/permissions.html

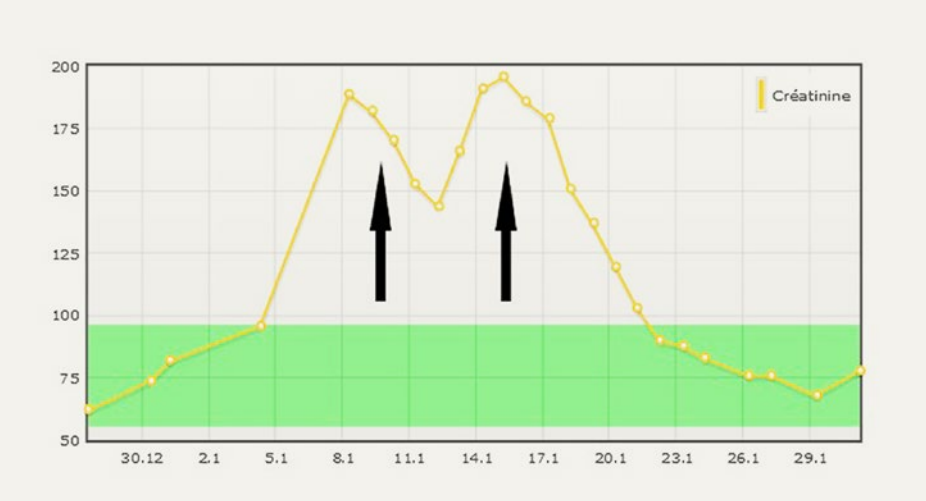

Figure 1: Blood creatinine in µmol/l (abscissa) during hospital stay (ordinate) in a 59-year-old patient with Child B9 alcoholic liver cirrhosis and hepatorenal syndrome. TerlipreFigure 1: Blood creatinine in µmol/l (abscissa) during hospital stay (ordinate) in a 59-year-old patient with Child B9 alcoholic liver cirrhosis and hepatorenal syndrome. Terlipressin initially improved renal function (arrows). When terlipressin was stopped following the first episode of acute pulmonary oedema (11.1), renal function worsened.

quiring needle puncture (>2 litres) followed by intravenous infusion of 80 g of albumin. Laboratory analysis of ascites showed no signs of spontaneous bacterial peritonitis.

On day 15, the patient developed acute oliguric renal failure AKIN II. Laboratory findings revealed creatinine of 153 µmol/l (55–96) and an eGFR of 42 ml/min (>60), which was attributed to hepatorenal syndrome (fig. 1). Intravenous treatment with terlipressin (1 mg over 1 minute four times daily) was started. Before the third terlipressin injection the patients was eupnoeic,

Intravenous furosemide was immediately started and the patient was transferred to the intensive care unit.

breathing ambient air with SpO_2 96% and the blood pressure was 126/82 mm Hg. One hour after injection, the patient suddenly experienced chest discomfort and dyspnoea. Within a few minutes he developed acute respiratory distress with respiratory rate 28/min and SpO_2 81%. Pulmonary auscultation found diffuse crackles. Glasgow coma scale score (GCS) was 14/15 (3-5-6), blood pressure 182/122 mm Hg, heart rate 111/min and temperature 37.4 °C.

Acute pulmonary oedema was suspected. Intravenous furosemide was immediately started and the patient was transferred to the intensive care unit (ICU). The state of consciousness rapidly deteriorated with a GCS of 3/15 and the patient was intubated. An ECG showed no sign of acute ischaemia and a prolongation of the corrected QT interval (Bazett) at 490 ms (400 ms at admission). The chest X-ray confirmed the diagnosis of acute pulmonary odema with possible concomitant nosocomial pneumonia. Nosocomial plurilobar aspiration pneumonia was suspected and piperacilin-tazobactam plus levofloxacin treatment was started. A diagnosis of concomitant aspiration pneumonia and acute pulmonary oedema secondary to volume overload after albumin infusion was made.

Propofol was used for sedation and norepinephrine was infused to maintain a mean blood pressure (MBP) of 65 mm Hg, while terlipressin therapy was stopped. The clinical condition rapidly improved. No microorganisms were found in bronchalveolar lavage fluid. The patient was weaned from mechanical ventilation and extubated after 48 hours with normal findings on lung auscultation and SpO_2 of 94% breathing ambient air. Due to persistence of hepatorenal syndrome (blood creatinine 196 µmol/l, urine volume 1500 ml/day, eGFR 31ml/min), intravenous terlipressin was restarted at the same dosage (1 mg over 1 minute q.i.d.) (fig. 1). The blood pressure was 115/65 mm Hg before the injection. Two hours after terlipressin injection, the patient suddenly developed arterial hypertension at 175/110 mm Hg (MBP 130 mm Hg) and acute dyspnoea with SpO_2 85% despite noninvasive ventilation. Diffuse pulmonary crackles were present on lung auscultation. Chest X-ray showed acute pulmonary oedema (fig. 2). Respiratory distress due to acute pulmonary oedema required a second intubation and intravenous furosemide. Terli-

The patient was extubated after 4 days.

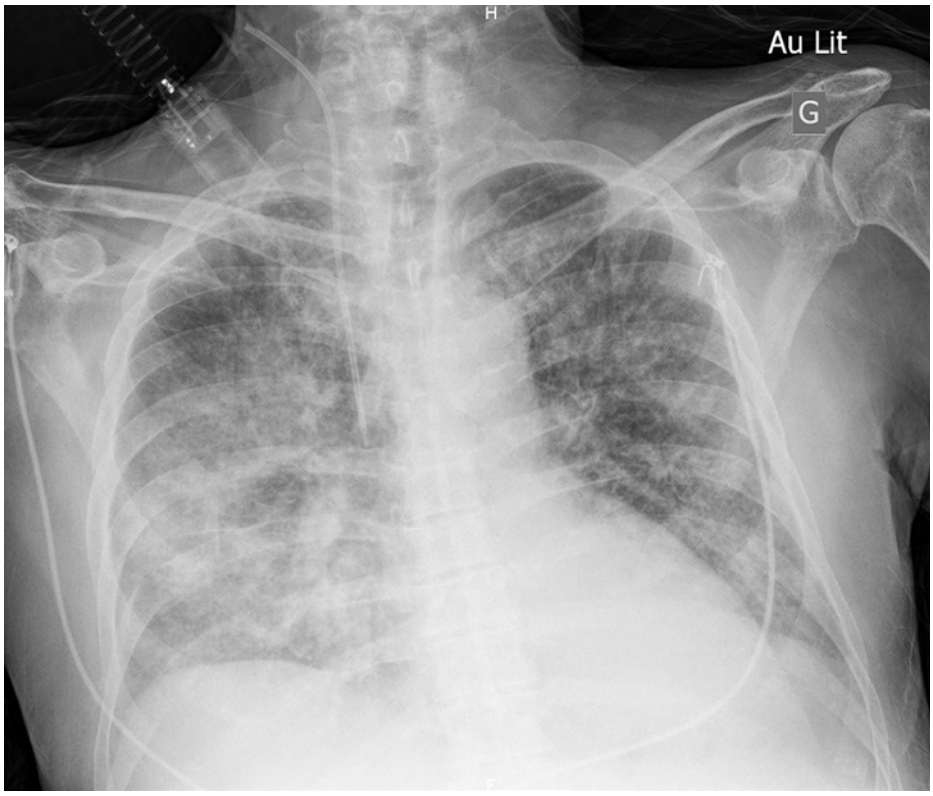

Figure 2: Chest X-ray of the relapsing episode of terlipressin-induced acute pulmonary oedema.

Published under the copyright license "Attribution – Non-Commercial – NoDerivatives 4.0". No commercial reuse without permission. See: http://emh.ch/en/services/permissions.html

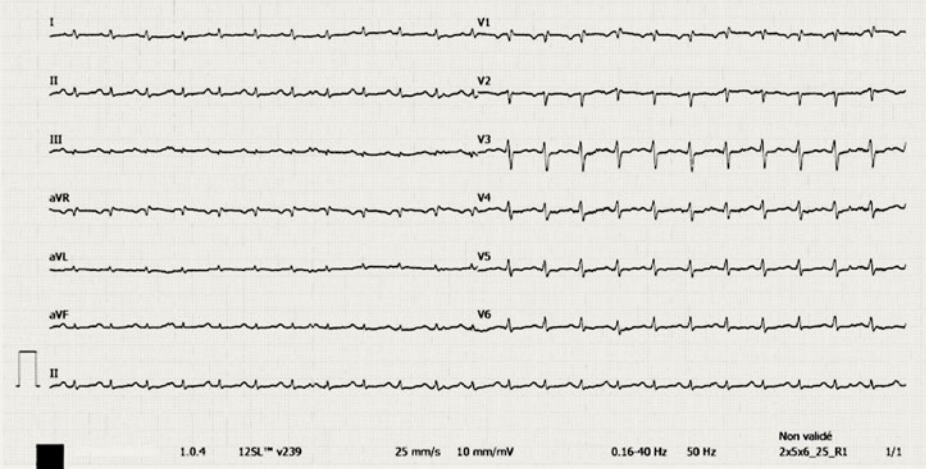

Figure 3: ECG during the second episode of acute pulmonary oedema, showing sinus tachycardia, without signs of acute ischaemia.

pressin therapy was stopped. An ECG showed no signs of ischaemia (fig. 3). Transthoracic echocardiography revealed left ventricular hypertrophy with preserved ejection fraction and diastolic dysfunction with restrictive filling pattern (mitral inflow E/A 3.5), without other anomalies (fig. 4). Although the patient was not known to have hypertension, the left ventricular hypertrophy and the relatively high blood pressure at admission (137/86 mm Hg) for the severity of his liver cirrhosis are suggestive of a chronic hypertensive heart disease. Oesophago-gastroscopy did not find oesophageal varices but showed gastritis due to portal hypertension, without active gastrointestinal tract tract bleeding. The patient was extubated after 4 days. Renal function normalised and the patient was discharged from the ICU after 18 days and from the hospital after 48 days.

Our final diagnosis was relapsing acute pulmonary oedema secondary to hypertensive crisis induced by terlipressin infusion with acute diastolic dysfunction.

Discussion

The hepatorenal syndrome is a life-threatening condition that occurs in patients with advanced liver cirrhosis. Two types of hepatorenal syndrome are described. Type 1 is commonly associated with alcoholic liver cirrhosis and is precipitated by events such as acute hepatitis, bleeding of oesophageal varices, or a systemic inflammatory response [7, 8]. Type 2 is characterised by functional renal failure. It usually appears in patients with refractory ascitis and is often associated with hydrosodium retention.

Hepatorenal syndrome, especially type 1, is associated with rapid deterioration of multiple organ functions and poor outcome [9]. It results from a complex haemodynamic dysregulation, which is initiated by portal hypertension, followed by systemic vasodilatation with arterial hypotension and renal vasoconstriction with acute oliguric renal failure.

Different treatments are recommended for hepatorenal syndrome, including infusion of vasoactive drugs with a vasoconstrictive effect aimed at lowering the arterial and venous pressure in the splanchnic circulation, intravenous infusion of albumin, transjugular intrahepatic portosystemic stent-shunt (TIPS) and extracorporeal albumin dialysis [10]. Vasoconstrictors are the most frequently used therapy. Terlipressin is the first-line vasoactive agent in Europe, owing to its superiority compared with midodrine [11] or placebo [12]. A recent randomised study showed that terlipressin was more effective than placebo in improving renal function, but described serious adverse events, including respiratory failure [13].

However, terlipressin is not available in the United States [14]. When terlipressin is not available, combination therapy with midodrine, octreotide and albumin is used for patients not in the intensive care unit. Terlipressin has been examined as a treatment for hepatorenal syndrome in several randomised trials and is preferred therapy in patients with hepatorenal syndrome who cannot receive norepinephrine (typically those not in an intensive care setting). As the efficacy of terlipressin and norepinephrine seems to be similar, norepinephrine is an alternative if terlipressin is not available [15, 16].

Adverse events such as abdominal cramping, headache, and tissue ischaemia (cutaneous, digestive, cardiac) have been associated with the vasoconstrictive effect of terlipressin [3, 17, 18]. Kulkarni et al. reviewed 25 cases of severe ischaemic side effects. Time to the development of ischaemia was 2.5 days after start of terlipressin treatment; 72% of patients

In patients at high risk for cardiovascular events, case reports have described cardiac adverse events related to terlipressin treatment

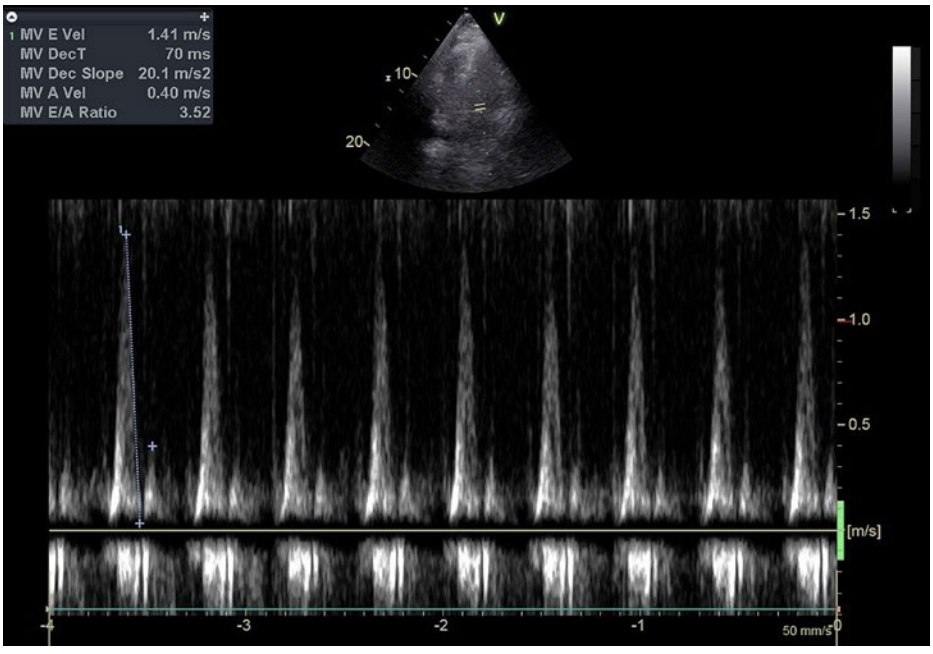

Figure 4: Transthoracic echocardiography showing acute diastolic dysfunction (mitral valve E/A ratio of 3.52). You will find a video file in the multimedia collection of Cardiovascular Medicine: https://cardiovascmed.ch/online-only-content.

Published under the copyright license "Attribution – Non-Commercial – NoDerivatives 4.0". No commercial reuse without permission. See: http://emh.ch/en/services/permissions.html

died from serious ischaemic side effects attributed to terlipressin [19]. In patients at high risk for cardiovascular events, case reports have described cardiac adverse events related to terlipressin treatment (myocardial ischaemia, cardiogenic shock, hypertension, bradycardia) [3, 20, 21].

However, such disastrous drug effects leading to an acute pulmonary oedema resulting from left ventricular diastolic dysfunction secondary to severe diastolic hypertension induced by the systemic vasoconstrictive effect of terlipressin have not been reported so far.

Terlipressin may have triggered an acute increase in both cardiac afterload through an increase of systemic vascular resistance, and preload through blood pool centralisation, both being responsible for acute pulmonary oedema in the context of a hypertrophied left ventricle with diastolic dysfunction [22].

Our patient had two episodes of acute pulmonary oedema less than 24 hours after initiating terlipressin treatment for hepatorenal syndrome. For the first episode of acute respiratory distress, nocosomial aspiration pneumonia associated with "capillary leak syndrome" was considered as differential diagnosis; however no infection was microbiologically documented despite culture of invasive samples of the lower respiratory tract. Hypervolaemia induced by the intravascular osmotic effect following infusion of 80 g of albumin after ascites puncture was another mechanism that was considered. Lack of albumin in the extravascular lung compartment might have contributed to the development of acute pulmonary oedema by increasing the alveolar oncotic pressure. Finally, the arterial hypertension induced by terlipressin was considered to have possibly precipitated acute pulmonary oedema, but the key pathophysiological role of this medication could not be immediately appreciated.

For the sudden, relapsing episode of acute pulmonary oedema, terlipressin therapy was the only identified precipitating factor. Follow up of the vital signs showed that 2 hours after terlipressin infusion, the patient developed arterial hypertension and oxygen desaturation. The chest X-ray confirmed acute pulmonary oedema. Transthoracic echocardiography revealed a mitral valve E/A ratio of 3.52 (restrictive filling pattern), compatible with left ventricular diastolic dysfunction. The acute pulmonary oedema occurring after intravenous terlipressin rechallenge, in the absence of other precipitating or confounding conditions and medications, demonstrates the causal mechanism associated with the vasoconstrictive effect of terlipressin on the systemic circulation.

Conclusion

Beside of its potential to induce myocardial ischaemia, terlipressin might trigger acute pulmonary oedema in cirrhotic patients with low systemic vascular resistance or in patients with latent left ventricular diastolic dysfunction through an increase in both preload and afterload. This first-line treatment for hepatorenal syndrome should only be used in intermediate or intensive care units, with continuous haemodynamic and respiratory monitoring. If arterial hypertension and/or desaturation occur, terlipressin must be immediately discontinued.

Disclosure statement

No financial support and no ptentail conflict of interest relevant to this article was reported.

Correspondence

Baudouin Bourlond, MD
Department of Medicine
Ensemble Hospitalier de la Côte (EHC)
Chemin du Crêt 2
CH-1110 Morges
bbourlond[at]gmail.com

References

1 Practice Guidelines Committee of American Association for Study of Liver Diseases, Practice Parameters Committee of American College of Gastroenterology, G Garcia-Tsao, AJ Sanyal, ND Grace, WD Carey. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol. 2007 Sep;102(9):2086–102. http://dx.doi.org/10.1111/j.1572-0241.2007.01481.x PubMed 0002-9270

2 AN Elzouki, A El-Menyar, E Ahmed, ME Elbadri, YZ Imam, BA Gurbanna. Terlipressin-induced severe left and right ventricular dysfunction in patient presented with upper gastrointestinal bleeding: case report and literature review. Am J Emerg Med. 2010 May;28(4):540.e1–6. http://dx.doi.org/10.1016/j.ajem.2009.08.012 PubMed 1532-8171

3 MY Lee, CS Chu, KT Lee, HC Lee, HM Su, KH Cheng Terlipressin-related acute myocardial infarction: a case report and literature review. Kaohsiung J Med Sci. 2004 Dec;20(12):604–8. http://dx.doi.org/10.1016/S1607-551X(09)70266-9 PubMed 1607-551X

4 T Ghatak, B Poddar, S Mahindra. Left ventricular failure and left ventricular inferior wall hypokinesia following terlipressin injection. Ann Card Anaesth. 2014 Jul-Sep;17(3):257–9. http://dx.doi.org/10.4103/0971-9784.135897 PubMed 0974-5181

5 J Medel, G Boccara, E Van de Steen, M Bertrand, G Godet, P Coriat. Terlipressin for treating intraoperative hypotension: can it unmask myocardial ischemia? Anesth Analg. 2001 Jul;93(1):53–5. http://dx.doi.org/10.1097/00000539-200107000-00012 PubMed 0003-2999

6 R Rosario, B Lalanne, P Lèbre, D Lepesan, JP Martelet, M Dupont [Myocardial infarction after injection of terlipressin for digestive hemorrhage]. Gastroenterol Clin Biol. 1996;20(8-9):712–3. PubMed 0399-8320

7 Gielen S, Delwaide J, Detry O, Honoré P, De Roover A, Meurisse M, et al. Rev Med Suisse 2002;2:22403. Diagnostic et traitement du syndrome hepatorenal

8 F Wong. Recent advances in our understanding of hepatorenal syndrome. Nat Rev Gastroenterol Hepatol. 2012 May;9(7):382–91. http://dx.doi.org/10.1038/nrgastro.2012.96 PubMed 1759-5053

9 F Salerno, A Gerbes, P Ginès, F Wong, V Arroyo. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007 Sep;56(9):1310–8. PubMed 0017-5749

10 SW Biggins, P Angeli, G Garcia-Tsao, P Ginès, SC Ling, MK Nadim Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Aug;74(2):1014–48. http://dx.doi.org/10.1002/hep.31884 PubMed 1527-3350

11 Italian Association for the Study of the Liver Study Group on Hepatorenal Syndrome, M Cavallin, PS Kamath, M Merli, S Fasolato, P Toniutto, F Salerno. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. Hepatology. 2015 Aug;62(2):567–74. http://dx.doi.org/10.1002/hep.27709 PubMed 1527-3350

12 CONFIRM Study Investigators, F Wong, SC Pappas, MP Curry, KR Reddy, RA Rubin, MK Porayko. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med. 2021 Mar;384(9):818–28. http://dx.doi.org/10.1056/NEJMoa2008290 PubMed 1533-4406

13 CONFIRM Study Investigators, F Wong, SC Pappas, MP Curry, KR Reddy, RA Rubin, MK Porayko. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med. 2021 Mar;384(9):818–28. http://dx.doi.org/10.1056/NEJMoa2008290 PubMed 1533-4406

14 SW Biggins, P Angeli, G Garcia-Tsao, P Ginès, SC Ling, MK Nadim Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Aug;74(2):1014–48. http://dx.doi.org/10.1002/hep.31884 PubMed 1527-3350

15 Wang H, Liu A, Bo W, Feng X, Hu Y. Terlipressin in the treatment of hepatorenal syndrome: A systematic review and meta-analysis. Medicine (Baltimore). 2018 Apr;97(16):e0431.

16 V Singh, S Ghosh, B Singh, P Kumar, N Sharma, A Bhalla Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. J Hepatol. 2012 Jun;56(6):1293–8. http://dx.doi.org/10.1016/j.jhep.2012.01.012 PubMed 1600-0641

17 P Sarma, G Muktesh, RS Singh, A Mishra, A Singh, RK Ruhela Terlipressin-Induced ischemic complications: A systematic review of published case reports. J Pharmacol Pharmacother. 2018;9(2):76–85. http://dx.doi.org/10.4103/jpp.JPP_23_18 0976-500X

18 P Sarma, G Muktesh, N Dhaka, R Ruhela, A Mishra, R Singh Terlipressin-induced Peripheral Ischemic Gangrene in a Diabetic Patient. J Pharmacol Pharmacother. 2017 Jul-Sep;8(3):148–50. PubMed 0976-500X

19 Kulkarni AV,Kumar P, Rao NP. Terlipressin-induced ischaemic skin necrosis. BMJ Case Rep. 2020 Jan;13(1).1757-790X

20 R Rosario, B Lalanne, P Lèbre, D Lepesan, JP Martelet, M Dupont Infarctus du myocarde après injection de terlipressine pour hémorragie digestive [Myocardial infarction after injection of terlipressin for digestive hemorrhage] [French.]. Gastroenterol Clin Biol. 1996;20(8-9):712–3. PubMed 0399-8320

21 A Krag, T Borup, S Møller, F Bendtsen. Efficacy and safety of terlipressin in cirrhotic patients with variceal bleeding or hepatorenal syndrome. Adv Ther. 2008 Nov;25(11):1105–40. http://dx.doi.org/10.1007/s12325-008-0118-7 PubMed 1865-8652

22 S Møller, EF Hansen, U Becker, K Brinch, JH Henriksen, F Bendtsen. Central and systemic haemodynamic effects of terlipressin in portal hypertensive patients. Liver. 2000 Feb;20(1):51–9. http://dx.doi.org/10.1034/j.1600-0676.2000.020001051.x PubMed 0106-9543

Published under the copyright license "Attribution – Non-Commercial – NoDerivatives 4.0". No commercial reuse without permission. See: http://emh.ch/en/services/permissions.html