Original Article

Adverse events of terlipressin in liver cirrhosis with acute gastrointestinal bleeding: a clinical pharmacist's real-world observational study

Jingqiao Zhang[1,2,3#], Xinmiao Zhou[4#], Haitao Zhao[5], Jiao Deng[2], Xingshun Qi[1]

[1]Department of Gastroenterology, [2]Department of Pharmacology, General Hospital of Shenyang Military Area, Shenyang 110840, China; [3]Postgraduate College, Shenyang Pharmaceutical University, Shenyang 110016, China; [4]Postgraduate College, Jinzhou Medical University, Jinzhou 121001, China; [5]Medical Ethical Committee, General Hospital of Shenyang Military Area, Shenyang 110840, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: J Zhang, X Qi; (V) Data analysis and interpretation: J Zhang, X Zhou, J Deng, X Qi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally as co-first authors.

Correspondence to: Dr. Xingshun Qi. Department of Gastroenterology, General Hospital of Shenyang Military Area, No. 83 Wenhua Road, Shenyang 110840, China. Email: xingshunqi@126.com.

Background: Terlipressin is the first-line treatment for the management of acute gastro-esophageal variceal bleeding and hepatorenal syndrome in liver cirrhosis. However, the incidence, characteristics, and outcomes of terlipressin related adverse events have not been defined.

Methods: We retrospectively reviewed all patients with cirrhosis and acute gastrointestinal bleeding who were treated with terlipressin at our department between January and March 2018. Except for the dose and duration of terlipressin, a clinical pharmacist observed and recorded the type, intervention, and outcomes of adverse events during terlipressin every day.

Results: A total of 24 patients were investigated. The incidence of adverse events during terlipressin was 50.0%. There were eight types of adverse events observed. Grade of adverse events was mild or moderate in most of patients. No lethal adverse event was observed. Six patients (25.0%) developed serum sodium concentration reduction. Two patients (8.3%) developed hyponatremia, in both of whom spontaneous resolution was achieved in the absence of any intervention. One patient developed tachycardia, in whom spontaneous resolution was achieved in the absence of any intervention. One patient developed abdominal pain, which was spontaneously resolved after the cessation of terlipressin.

Conclusions: In our everyday clinical practice, terlipressin related adverse events are common, but often reversible. Further large scale observational studies should be necessary to confirm our findings.

Keywords: Terlipressin; adverse event; bleeding; hyponatremia; cirrhosis

Received: 02 June 2018; Accepted: 13 June 2018; Published: 19 June 2018.

doi: 10.21037/dmr.2018.06.02

View this article at: http://dx.doi.org/10.21037/dmr.2018.06.02

Introduction

Terlipressin is a vasopressin analogue that has a synthetic 12 amino acid peptide (1). Terlipressin acts through the V1 receptors which can include splanchnic vasoconstriction, increase arterial blood volume, and reduce portal pressure. It acts through the V2 receptors which can deactivate renal and systemic vasoconstrictor systems, increase glomerular filtration rate, and improve renal perfusion and function (2). Currently, terlipressin is the first-line treatment for the management of acute gastro-esophageal variceal bleeding and hepatorenal syndrome (3,4).

Generally, terlipressin has a good tolerance with a lower

incidence of serious adverse events (5). Common terlipressin related adverse events are mild or moderate, such as abdominal pain and diarrhea. Serious adverse events, such as hyponatremia, are rare due to increased cyclic adenosine monophosphate concentration, activated phosphorylation of the aquaporin-2, increased water permeability, and decreased plasma osmolality (6-10).

It is important for physicians to recognize drug related adverse events as early as possible. The physicians could provide the prophylactic measures appropriately to avoid the development of adverse events. Once adverse events developed, the physicians could employ the therapeutic measures immediately to avoid the progression of adverse events. Thus, the aims of this study are to explore the incidence, characteristics, and outcomes of adverse events during treatment with terlipressin in patients with liver cirrhosis.

Methods

This was a retrospective, single-center study. A total of 24 patients with cirrhosis and acute gastrointestinal bleeding who were consecutively treated with terlipressin at the Department of Gastroenterology of our hospital between January 2018 and March 2018, were retrospectively enrolled. The following data were collected: age, sex, etiology of cirrhosis, Child-Pugh score, model of end stage liver disease (MELD) score, total bilirubin and direct bilirubin, alanine aminotransaminase, aspartate aminotransaminase, white blood cell, hemoglobin, neutrophils, lymphocyte, platelet, D-dimer, fibrinogen, prothrombin time, activated partial thromboplastin time, international normalized ratio, blood urea nitrogen, creatinine, potassium, and sodium.

A clinical pharmacist (J Zhang) observed and recorded the type, intervention, and outcomes of adverse events during terlipressin in these patients treated with terlipressin every day. In the cases of uncertainty regarding adverse events, she will discuss with another clinical pharmacist (J Deng) and a vice-chief physician (X Qi).

Grade of adverse events was assessed as follows: grade I (mild), awareness of signs or symptoms, but no disruption of usual activity; grade II (moderate), event sufficient to affect usual activity (disturbing); grade III (severe), inability to work or perform usual activity (unacceptable) (11). The following attribution categories were used by the Common Terminology Criteria for assessment of adverse events 4.0 (11): definite, adverse event is clearly related to agents; probable, adverse event is likely related to agents; possible, adverse event may be related to agents; unlikely, adverse event is doubtfully related to agents; unrelated, adverse event is clearly not related to agents. Serum sodium concentration reduction was defined as a decrease in serum sodium level of >5 mmol/L from the baseline. Hyponatremia was defined as a serum sodium concentration of <130 mmol/L.

Data were expressed as mean ± standard deviation and median (range) for continuous variables and frequency (percentage) for categorical variables. Data were analyzed using SPSS 22.0 statistical software.

Results

Baseline characteristics

A total of 24 patients (16 males and 8 females) were included (*Table 1*). The mean patient age was 56.5±9.4 years (range: 38.0–71.0 years). Only one patient also had hepatorenal syndrome. The mean Child-Pugh score was 8.1±1.9 (range: 5.0–13.0). The mean MELD score was 5.7±4.8 (range: –4.9–17.9). The mean serum creatinine was 67.2±37.2 μmol/L (range: 1.2–143.6 μmol/L). The mean serum sodium was 139.8±6.6 mmol/L (range: 127.0–159.0 mmol/L).

Terlipressin

The mean total dose of terlipressin was 12.3±8.3 mg (range: 4.0–28.0 mg). Twenty-two patients were administered by continuous intravenous infusion alone. Two patients were administered by intravenous bolus followed continuous intravenous infusion. The mean duration of terlipressin was 3.1±2.2 days (range: 1.0–9.0 days).

Adverse events

The total incidence of adverse events was 50.0% (12/24) (*Tables 2,3*). There were eight types of adverse events observed.

Six patients (25.0%) developed serum sodium concentration reduction. All of them did not receive any intervention. Among them, no further change was observed in 5 patients, and spontaneous resolution was observed in 1 patient.

Two patients (8.3%) developed hyponatremia. Spontaneous resolution was observed in both patients without any intervention.

One patient developed tachycardia. Spontaneous

Table 1 Baseline characteristics of the 24 patients treated with terlipressin

Variables	Mean ± SD or frequency (percentage)	Median (range)
Age (years)	56.5±9.4	56.5 (38.0–71.0)
Sex (male/female)	16 (66.7%)/8 (33.3%)	
Etiology		
Hepatitis B	11 (45.8%)	
Hepatitis C	1 (4.2%)	
Alcohol abuse	4 (16.7%)	
Autoimmune-related	1 (4.2%)	
Drug-related	2 (8.3%)	
Unknown	5 (20.8%)	
Hepatic encephalopathy	2 (8.3%)	
Hepatocellular carcinoma	5 (20.8%)	
Child-Pugh score	8.1±1.9	8 (5.0–13.0)
MELD score	5.7±4.8	5.1 (–4.9–17.9)
Hemoglobin (g/L)	82.3±22.6	83.5 (32.0–129.0)
White blood cell (10^9/L)	5.4±3.9	4.9 (1.2–20.1)
Neutrophils (10^9/L)	4.0±3.3	3.6 (0.8–16.3)
Lymphocyte (10^9/L)	2.7±5.4	0.8 (0.2–23.0)
Platelet (10^9/L)	93.1±88.7	68.5 (15.0–446.0)
Serum total bilirubin (μmol/L)	38.2±38.7	24.1 (7.2–153.3)
Serum direct bilirubin (μmol/L)	21.7±28.3	12.7 (3.9–123.3)
Alanine aminotransaminase (U/L)	34.6±30.5	30.2 (2.5–157.1)
Aspartate aminotransaminase (U/L)	37.1±20.6	36.3 (2.5–87.2)
Albumin (g/L)	28.8±7.3	29.1 (5.7–38.8)
Creatinine (μmol/L)	67.2±37.2	57.2 (1.2–143.6)
Blood urea nitrogen (mmol/L)	8.7±4.9	7.8 (1.6–21.2)
Serum potassium (mmol/L)	3.9±0.8	3.9 (1.4–5.5)
Serum sodium (mmol/L)	139.8±6.6	139.7 (127.0–159.0)
D-dimer (mg/L)	3.6±5.9	1.0 (0.2–21.2)
Fibrinogen (g/L)	2.0±0.8	1.8 (0.9–4.2)
Prothrombin time (s)	20.2±6.2	18.1 (14.4–36.0)
Activated partial thromboplastin time (s)	42.9±8.2	41.3 (30.0–59.5)
International normalized ratio	1.7±0.7	1.5 (1.1–3.5)
Cumulative defined daily dose (cDDD)	1.0±0.7	0.8 (0.3–2.3)
Total dose of terlipressin (mg)	12.3±8.3	10 (4.0–28.0)
Duration of terlipressin (days)	3.1±2.2	2.5 (1.0–9.0)

Table 2 Adverse events

Patient	Adverse events	Degree of probability	Grade	Intervention	Outcome
No. 1	Serum sodium concentration reduction	Possible	1	No intervention	Stable
No. 2	Abdominal pain	Definite	2	Cessation of terlipressin	Spontaneous improvement
	Serum sodium concentration reduction	Possible	1	No intervention	Stable
No. 3	Serum sodium concentration reduction	Possible	1	No intervention	Stable
No. 4	Serum sodium concentration reduction	Possible	1	No intervention	Stable
No. 5	Diarrhea	Probable	1	No intervention	Spontaneous improvement
No. 6	Dizziness	Definite	2	Cessation of terlipressin	Spontaneous improvement
No. 7	Serum sodium concentration reduction	Possible	1	No intervention	Stable
No. 8	Diarrhea	Probable	1	No intervention	Spontaneous improvement
	Nausea	Probable	1	No intervention	Spontaneous improvement
	Vomiting	Probable	1	No intervention	Spontaneous improvement
No. 9	Serum sodium concentration reduction	Definite	1	No intervention	Spontaneous improvement
No. 10	Hyponatremia	Definite	3	No intervention	Spontaneous improvement
No. 11	Tachycardia	Probable	3	No intervention	Spontaneous improvement
No. 12	Hyponatremia	Probable	3	No intervention	Spontaneous improvement

Table 3 Rate of adverse events

Adverse events	Number (%)
Abdominal pain	1 (4.2)
Diarrhea	2 (8.3)
Dizziness	1 (4.2)
Nausea	1 (4.2)
Vomiting	1 (4.2)
Serum sodium concentration reduction	6 (25.0)
Hyponatremia	2 (8.3)
Tachycardia	1 (4.2)

resolution was observed in this patient with no intervention.

One patient developed abdominal pain. This adverse event was moderate and resolved spontaneously after cessation of terlipressin.

Discussion

Adverse events can develop during use of terlipressin (12,13). Sometimes, they are life-threatening. According to the drug instructions, terlipressin should be given by intravenous bolus at a dose of 2 mg followed by intravenous infusion at a dose of 1–2 mg every 4–6 hours. However, a recent randomized controlled trial (14) suggested that continuous intravenous infusion of terlipressin would lead to less adverse events than intravenous bolus in cirrhotic patients with hepatorenal syndrome. Similarly, in our study, terlipressin was frequently given by continuous intravenous infusion, but not intravenous bolus.

We found that half of patients treated with terlipressin might develop drug-related adverse events, but none of them was lethal. This might be explained by the fact that the dosage of terlipressin was often minimized in our study. Serum sodium concentration reduction and hyponatremia were the most common adverse events (15). Notably, most of terlipressin related adverse events were self-limiting (13,15-18).

We observed one case developing abdominal pain after intravenous bolus of terlipressin, which might be associated with intestinal ischemia. We observed one case developing dizziness after continuous intravenous infusion of terlipressin, which might be associated with a sudden increase of blood pressure and splanchnic vasoconstriction. We also observed one case developing tachycardia after

continuous intravenous infusion of terlipressin. This seemed to be inconsistent with the drug instructions that the incidence of bradycardia was 0.1–1%, but no tachycardia was recorded.

Drug instructions suggests that blood pressure elevation and pallor were common (incidence is 1–10%). Blood pressure elevation can be self-limiting once antihypertensive drugs are given (19). However, in our present work, neither blood pressure elevation nor pallor was observed during the treatment with terlipressin. This phenomenon can be explained by the fact that all of our patients included had acute gastrointestinal bleeding and presented with pallor and relatively lower blood pressure. Thus, the two adverse events are often masked by their actual clinical conditions. It has been reported that the incidence of cardiovascular adverse events, including myocardial ischemia, myocardial infarction, left ventricular failure, arrhythmia, and dyspnea, was <0.01%. However, in our present work, neither dyspnea nor cardiovascular abnormality was observed. Additionally, we did not observe any adverse events in respiratory system and skin.

Conclusions

Based on a clinical pharmacist's everyday observation, most of terlipressin related adverse events were mild or moderate, which can be resolved spontaneously without any intervention. However, a small sample size and a single-center observation were the major limitations of our study. We should need further multicenter data with larger sample size.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr.2018.06.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethical Committee, General Hospital of Shenyang Military Area [No. k(2018)17]. The written informed consent was waived due to the retrospective nature of the study.

References

1. Papaluca T, Gow P. Terlipressin: Current and emerging indications in chronic liver disease. J Gastroenterol Hepatol 2018;33:591-8.
2. Colson PH, Virsolvy A, Gaudard P, et al. Terlipressin, a vasoactive prodrug recommended in hepatorenal syndrome, is an agonist of human V1, V2 and V1B receptors: Implications for its safety profile. Pharmacol Res 2016;113:257-64.
3. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev 2003;(1):CD002147.
4. Gluud LL, Christensen K, Christensen E, et al. Terlipressin for hepatorenal syndrome. Cochrane Database Syst Rev 2012;(9):CD005162.
5. Krag A, Borup T, Moller S, et al. Efficacy and safety of terlipressin in cirrhotic patients with variceal bleeding or hepatorenal syndrome. Adv Ther 2008;25:1105-40.
6. Piano S, Schmidt HH, Ariza X, et al. Association Between Grade of Acute on Chronic Liver Failure and Response to Terlipressin and Albumin in Patients With Hepatorenal Syndrome. Clin Gastroenterol Hepatol 2018. [Epub ahead of print].
7. Seo YS, Park SY, Kim MY, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014;60:954-63.
8. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. Gastroenterology 2002;122:923-30.
9. Halimi C, Bonnard P, Bernard B, et al. Effect of

terlipressin (Glypressin) on hepatorenal syndrome in cirrhotic patients: results of a multicentre pilot study. Eur J Gastroenterol Hepatol 2002;14:153-8.
10. Escorsell A, Ruiz del Arbol L, Planas R, et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. Hepatology 2000;32:471-6.
11. Chen AP, Setser A, Anadkat MJ, et al. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. J Am Acad Dermatol 2012;67:1025-39.
12. Narahara Y, Kanazawa H, Sakamoto C, et al. The efficacy and safety of terlipressin and albumin in patients with type 1 hepatorenal syndrome: a multicenter, open-label, explorative study. J Gastroenterol 2012;47:313-20.
13. Testro AG, Wongseelashote S, Angus PW, et al. Long-term outcome of patients treated with terlipressin for types 1 and 2 hepatorenal syndrome. J Gastroenterol Hepatol 2008;23:1535-40.
14. Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology 2016;63:983-92.
15. Kang YJ, Bae EJ, Hwang K, et al. Initial serum sodium concentration determines the decrease in sodium level after terlipressin administration in patients with liver cirrhosis. Springerplus 2013;2:519.
16. Narahara Y, Kanazawa H, Taki Y, et al. Effects of terlipressin on systemic, hepatic and renal hemodynamics in patients with cirrhosis. J Gastroenterol Hepatol 2009;24:1791-7.
17. Soderlund C, Magnusson I, Torngren S, et al. Terlipressin (triglycyl-lysine vasopressin) controls acute bleeding oesophageal varices. A double-blind, randomized, placebo-controlled trial. Scand J Gastroenterol 1990;25:622-30.
18. Feu F, Ruiz del Arbol L, Banares R, et al. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. Variceal Bleeding Study Group. Gastroenterology 1996;111:1291-9.
19. Romero G, Kravetz D, Argonz J, et al. Terlipressin is more effective in decreasing variceal pressure than portal pressure in cirrhotic patients. J Hepatol 2000;32:419-25.

doi: 10.21037/dmr.2018.06.02
Cite this article as: Zhang J, Zhou X, Zhao H, Deng J, Qi X. Adverse events of terlipressin in liver cirrhosis with acute gastrointestinal bleeding: a clinical pharmacist's real-world observational study. Dig Med Res 2018;1:2.