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Case Report

Successful administration of clazosentan in subarachnoid hemorrhage patient with severe heart failure

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ABSTRACT

Background: Clazosentan, an endothelin receptor antagonist, has been shown to prevent cerebral vasospasms following subarachnoid hemorrhage (SAH) effectively. However, clazosentan-induced pulmonary edema is a frequently reported adverse effect and a primary reason for discontinuing treatment. The presence of preexisting heart conditions predisposes patients to severe pulmonary edema; thus, the administration of clazosentan is generally contraindicated.

Case Description: We report the successful administration of clazosentan in a 58-year-old female patient with SAH and severe heart failure (Takotsubo cardiomyopathy). The patient initially presented with a ruptured left internal carotid posterior communicating artery aneurysm, leading to SAH. She successfully underwent neck clipping, and postoperative treatment to prevent cerebral vasospasm, including clazosentan, was initiated. Following the emergency surgical intervention, she exhibited pulmonary edema and diffused left ventricular hypokinesis with an ejection fraction of 10–20%. Although drug-induced pulmonary edema emerged after the administration of clazosentan, tailored fluid management based on daily cardiac function and ventilator management in response to pulmonary edema enabled the completion of a 2-week clazosentan therapy regimen. This approach guaranteed the patient's stability throughout the treatment period. Neither cerebral vasospasm nor cardiopulmonary complications were observed.

Conclusion: This case highlights the importance of a multidisciplinary approach in managing complex patients with severe cardiac comorbidities undergoing clazosentan therapy.

Keywords: Cerebral vasospasm, Clazosentan, Pulmonary edema, Subarachnoid hemorrhage, Takotsubo cardiomyopathy

INTRODUCTION

Subarachnoid hemorrhage (SAH) is often associated with cerebral vasospasm, which can lead to severe cerebral infarctions if not properly managed.[5,9] Preventing cerebral vasospasm is thus critical in the postoperative care of SAH patients. Clazosentan, an endothelin receptor antagonist, has been recognized for its potential to mitigate delayed cerebral vasospasm following SAH.[1,10] Despite its approval in Japan in 2022 and its recommendation as a Grade B treatment, clazosentan has not been approved in other countries, and its clinical use remains limited.[6,14] Clazosentan therapy frequently comes with adverse effects, especially fluid retention and pulmonary edema, which can complicate its continued use.[8]

The management of pulmonary edema involves careful fluid and respiratory management, with a significant reliance on cardiac function. Pulmonary edema is particularly challenging to manage in patients with preexisting severe heart conditions, such as Takotsubo cardiomyopathy.[12] Typically, clazosentan is not administered to patients with severe heart failure due to the high risk of exacerbating fluid retention and pulmonary complications.[4] In this report, we present a case of a patient with severe heart failure due to Takotsubo cardiomyopathy who successfully completed a 2-week regimen of clazosentan, effectively preventing cerebral vasospasm without significant complications. This case highlights that, with careful fluid and respiratory management under close monitoring, clazosentan can be safely administered even to patients with severe heart conditions.

CASE DESCRIPTION

A 58-year-old female with a medical history of asthma presented with a sudden onset of unconsciousness and was transported to our emergency department. On arrival, her Glasgow coma scale score was E1V1M4, and neurological examination revealed right hemiparesis. A contrast-enhanced computed tomography scan of the head showed a SAH due to a ruptured left internal carotid-posterior communicating artery aneurysm, accompanied by cerebral hematoma (World Federation of Neurosurgical Societies Grade IV, Fisher IV) [Figure 1]. The patient underwent neck clipping surgery and decompressive craniectomy, followed by admission to the intensive care unit (ICU).

On admission to the ICU, echocardiography showed diffuse left ventricular hypokinesis with an ejection fraction (EF) of 10–20%. No significant valvular abnormalities were observed [Figure 2]. The patient had pink frothy sputum, and Takotsubo cardiomyopathy was suspected due to stress-induced cardiomyopathy and decreased pulse pressure. A chest X-ray examination demonstrated a butterfly shadow and heart enlargement, consistent with cardiogenic pulmonary edema [Figure 3].

On postoperative Day 1, clazosentan (10 mg/h) and fasudil (30 mg IV infusion every 8 h) were initiated to prevent cerebral vasospasm. Due to the risk of fluid retention associated with clazosentan, daily cardiac ultrasound, chest X-rays, and blood tests were used to determine daily fluid balance goals and manage the patient's condition [Figure 4]. Comprehensive cardiac assessments were performed each day, including measurements of EF, left ventricular outflow tract velocity-time integral, and E/e' ratio. Diuretics such as furosemide were administered to achieve these fluid balance objectives. Early postoperative enteral nutrition was initiated through a nasogastric tube.

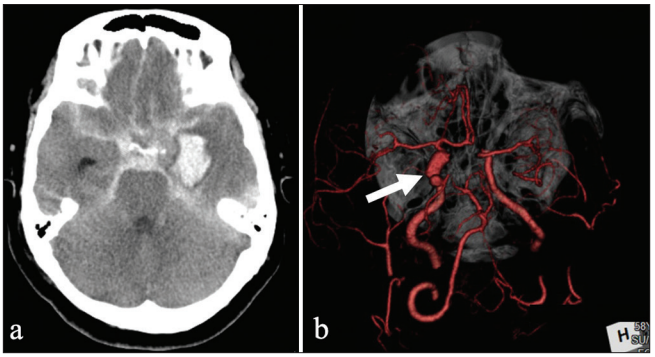

Figure 1: (a) Axial view of CT scan demonstrates subarachnoid hemorrhage with left temporal lobar hemorrhage. (b) A three-dimensional contrast-enhanced CT scan shows intracranial artery, with the white arrow indicating the left Internal carotid-posterior communicating (ICPC) ruptured aneurysm.

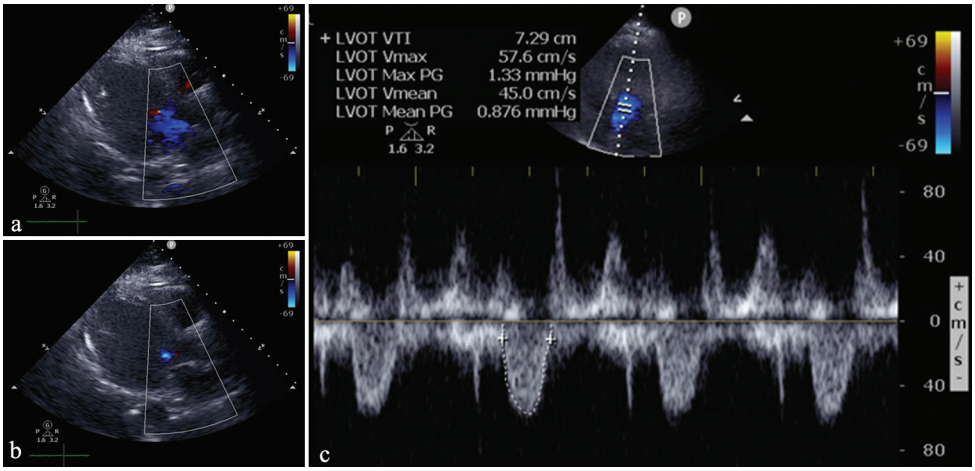

Figure 2: (a and b) Trans-thoracic echocardiography in diastolic phase and systolic phase indicating diffuse left ventricular hypokinesis with an ejection fraction (EF) of 10-20%. (c) Left ventricular outflow tract (LVOT) velocity-time integral (VTI) shows 7.29 cm, indicating low cardiac output.

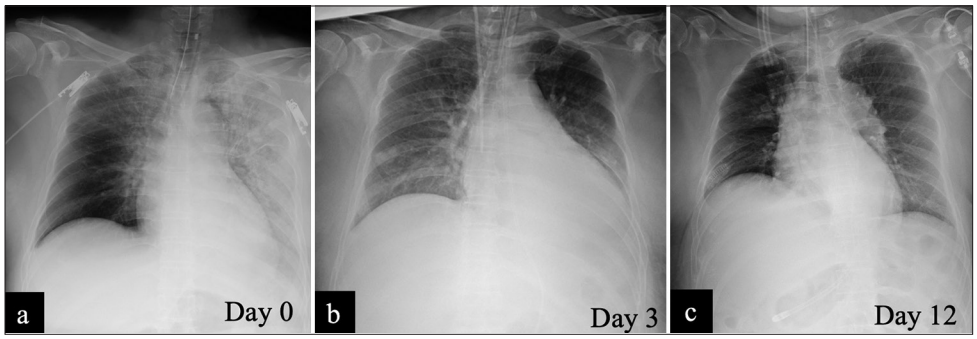

Figure 3: (a) Chest X-ray on Day 0 shows a butterfly shadow indicating cardiogenic pulmonary edema. (b) Chest X-ray on Day 3 shows an enhanced shadow in the right hilum, indicating drug-induced pulmonary edema. (c) Chest X-ray on Day 12 shows improvement in pulmonary edema and reduced heart size.

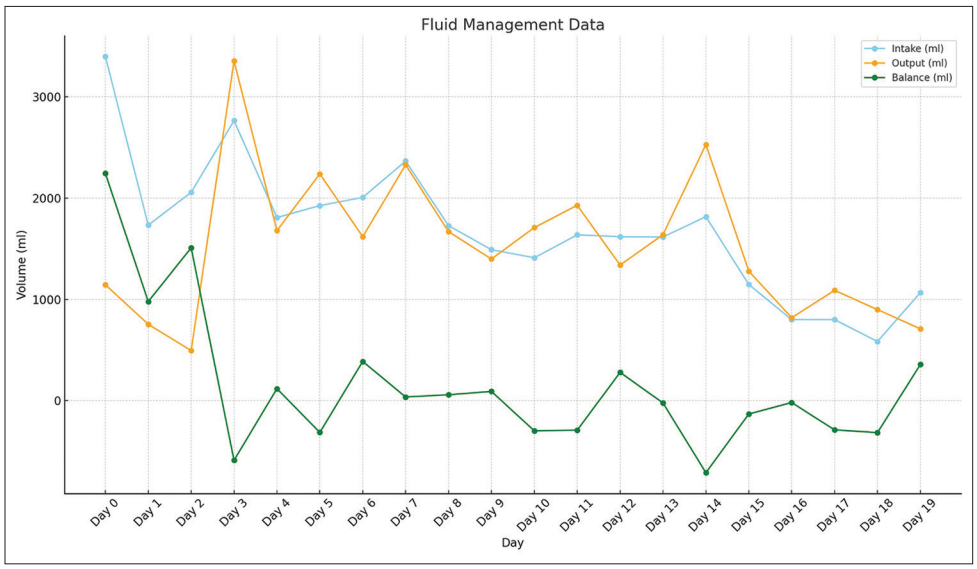

Figure 4: Graph showing daily fluid management. Daily fluid balance goals were set, prioritizing the improvement of pulmonary edema over hypervolemia for cerebral vasospasm.

On postoperative day 3, drug-induced pulmonary edema was observed. Managing pulmonary edema was prioritized over hypervolemia for cerebral vasospasm. Mechanical ventilation was continued, and ventilator setting adjustments were made to address the initial cardiogenic pulmonary edema and Takotsubo cardiomyopathy. Dobutamine was used to improve hemodynamics, significantly enhancing cardiac function, with the EF increasing to 60%.

On postoperative day 10, cerebral angiography was performed to assess for cerebral vasospasm, and no significant vasospasm was detected [Figure 5]. In addition to cerebral angiography, intracranial Doppler was utilized to evaluate and confirm the absence of vasospasm as needed. Clazosentan was administered for 2 weeks, during which no significant cerebral vasospasm was observed.

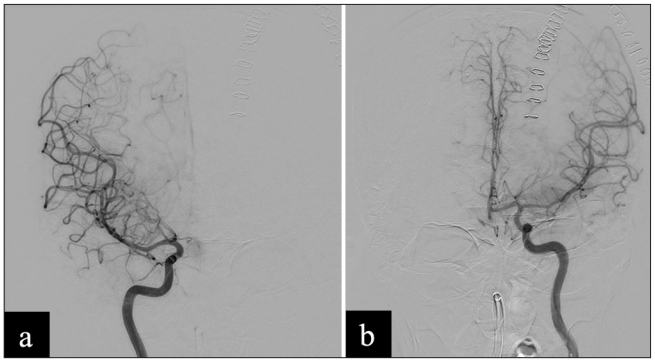

Figure 5: (a) Cerebral angiography of the left internal carotid artery showing no signs of vasospasm. (b) Cerebral angiography of the right internal carotid artery showing no signs of vasospasm.

Although the patient experienced drug-induced pulmonary edema, it was ultimately managed through meticulous fluid

management, preventing any worsening of the condition. Mechanical ventilation was successfully weaned, and the patient was extubated on day 19. Following a cranioplasty, the patient was transferred to a rehabilitation hospital on day 50. This case demonstrates that, with careful management and monitoring, clazosentan can be safely administered even in patients with severe cardiac conditions.

DISCUSSION

The prevention of cerebral vasospasm following SAH is crucial, as it significantly impacts the morbidity and mortality associated with this condition.[15] Due to the absence of nimodipine, a dihydropyridine calcium channel blocker, approval in Japan, the therapeutic options for managing delayed cerebral vasospasm are limited to fasudil hydrochloride and ozagrel sodium.[11,13] Additional treatment strategies include maintaining plasma volume and employing hyperdynamic therapy.[2] Clazosentan, which inhibits endothelin-mediated cerebral vasospasms, has shown efficacy in reducing the incidence of cerebral vasospasm and associated morbidity at 6 weeks, as demonstrated in phase 3 trials.[1] Consequently, it received initial approval for clinical use in Japan in 2022.[7] The introduction of clazosentan into clinical practice offers hope for decreasing the frequency of vasospasm in SAH patients.

However, clazosentan therapy is accompanied by notable adverse effects, primarily fluid retention.[16] Among these, pulmonary edema is a severe complication that can necessitate discontinuation of the therapy, causing clinicians to either avoid initiating clazosentan or stop the treatment early when pulmonary edema develops.[4,8] This underscores the critical need for effective fluid management and close monitoring during clazosentan therapy to mitigate these risks.

Given the importance of preventing cerebral vasospasm, it is essential to continue clazosentan therapy despite its potential adverse effects. Patients with preexisting heart failure or those who have developed Takotsubo cardiomyopathy due to SAH have a high risk of pulmonary edema.[3] Intensive care management that includes continuous monitoring of cardiac function, precise fluid balance management, and appropriate use of diuretics is necessary to ensure the safe administration of clazosentan in these patients.

In this case, the patient exhibited severe left ventricular dysfunction with an EF of 10–20% due to stress-induced cardiomyopathy and cardiogenic pulmonary edema at the initiation of clazosentan therapy. Despite the high risk of exacerbating cardiogenic pulmonary edema, clazosentan was administered. During the course of treatment, the patient developed drug-induced pulmonary edema but continued clazosentan therapy. Pulmonary edema was managed effectively by careful use of dobutamine to support cardiac function, strict fluid management, and optimized mechanical ventilation settings. Daily fluid management goals were determined based on cumulative fluid balance, the previous day's balance target achievement, and findings from echocardiography and chest X-rays. Tailored management for each patient enables the completion of clazosentan therapy without significant complications.

This case demonstrates that even in patients with severe heart failure, clazosentan therapy can be completed with diligent and comprehensive management. The occurrence of drug-induced pulmonary edema, while challenging, can be mitigated with appropriate interventions. Even if it occurs, maintaining circulation and respiratory function allows for the continuation of clazosentan therapy. Conventionally, hypervolemia has been recommended for the prevention of vasospasm; however, in the context of clazosentan therapy, maintaining euvolemia or, in certain cases, hypovolemia is more advantageous.[2] While the pulmonary edema typically resolves once the clazosentan therapy is completed, cerebral infarction due to vasospasm is irreversible. Thus, prioritizing the completion of clazosentan therapy during the critical period is justified, ultimately leading to the prevention of cerebral vasospasm. The successful outcome in this high-risk patient underscores the potential for broader use of clazosentan in preventing cerebral vasospasm, even among patients with complex comorbidities, which provided that they are managed with comprehensive care strategies.

CONCLUSION

While clazosentan is effective in preventing cerebral vasospasm after SAH, its use in patients with severe heart conditions requires careful management. We were able to prevent cerebral vasospasm using clazosentan in a high-risk patient with rigorous monitoring and comprehensive supportive care, including optimal fluid management and cardiac support. The successful outcome highlights the possibility for broader application of clazosentan in preventing cerebral vasospasm through tailored and comprehensive care strategies.

Ethical approval

The research/study was approved by the Institutional Review Board at Tokyo Bay Urayasu Ichikawa Medical Center, number 940, dated June 28, 2024.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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