Intrathecal Baclofen Toxicity and Deep Coma in Minutes

Yusuf Tunalı, MD¹; Hakan Hanimoglu, MD²; Taner Tanriverdi, MD²; Lale Hanci, MD³; Murat Hanci, MD²

¹Istanbul University, Cerrahpasa Medical Faculty, Department of Anesthesiology, Istanbul, Turkey;

²Istanbul University, Cerrahpasa Medical Faculty, Department of Neurosurgery, Istanbul, Turkey;

³Balta Limani, Bone and Joint Disorders Research and Education Hospital, Istanbul, Turkey

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Abstract

Background/Objective: In recent years, intrathecal baclofen (ITB) treatment in patients with refractory spasticity has been accepted as an effective therapy. However, this treatment modality may cause life-threatening complications. This report describes the clinical presentation, unfamiliar dilemmas, and treatment of a patient with ITB toxicity and raises awareness of problems that may arise.

Methods: A 33-year-old man with refractory spasticity due to diffuse white matter injury was admitted for ITB treatment. The patient had respiratory difficulty followed by a generalized seizure and developed coma minutes after the drug administration. The patient was transferred into an intensive care unit immediately and managed accordingly.

Results: After proper management, the patient was followed and continued to receive ITB treatment.

Conclusions: ITB therapy is a very effective method of rehabilitation and medication in patients with refractory spasticity, but physicians must be aware of the serious complications that may develop just minutes after the drug is administered. Although safe, baclofen pumps are nevertheless mechanical devices that may malfunction. Therefore, physicians should be mindful of the possibility of life-threatening complications that may develop and lead to a patient's death if proper treatment is not performed.

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INTRODUCTION

Baclofen is a skeletal muscle relaxant acting centrally as a presynaptic gamma-amino-butyric acid-B (GABA-B) receptor agonist (1). In recent years, it has been proved that intrathecally administered baclofen has beneficial effects in the treatment of severe and medically refractory spasticity (2). Intrathecal baclofen (ITB) therapy has been approved by the US Food and Drug Administration for the treatment of severe spasticity of either spinal or cerebral origin in cases of refractoriness to oral medications or when oral medications are not tolerated (3). With the increased use of ITB pumps, it has become necessary for physicians to become more familiar with the possible untoward effects of their use, namely, pump malfunctions and the possible overdose of baclofen intrathecally (1). At higher doses, baclofen causes toxic effects ranging from increased somnolence to hemody-

namic instability and even death. Patients should be monitored especially carefully after the administration of baclofen.

Our aim in this paper is to present a case in which signs of acute toxicity and deep coma occurred just minutes after ITB treatment and to describe the clinical presentation, unfamiliar dilemmas, and subsequent management.

CASE REPORT

A 33-year-old man was referred to our clinic because of spasticity that had not responded to a combination of physical therapy and oral medication. His medical history revealed a head injury due to a motor vehicle accident 14 months prior, and his Glasgow Coma Score (GCS) was 5/15. Diagnostic work-up at that time showed diffuse axonal injury, and the patient was managed in the intensive care unit (ICU) with mechanical ventilation. The patient's neurological status progressively improved, and his GCS was 13/15 at the time of his transfer to the ward. However, the patient had spastic tetraparesis, of which the lower extremities were more paretic than the upper

Please address correspondence to Murat Hanci, MD, PO Box 9, 34301 Cerrahpasa, Istanbul, Turkey; phone: +90.532. 243.39.46; fax: +90.212.414.35.76 (email: murath@istanbul.edu.tr).

ones and the overall muscle tone and deep tendon reflexes were increased. Afterwards, he was discharged from the hospital. Despite the aggressive physical therapy and high dosage of oral medication, the spasticity worsened progressively and he was referred to us for ITB therapy. His neurological examination revealed severe spasticity in all extremities.

A drug pump was implanted (Archimedes Implantable Constant-Flow Pump, filling volume 60 mL and flow rate 1.92 mL/24 h; Codman, Raynham, MA). The postoperative period was uneventful, and after the surgical wound healed, 20 mL of baclofen (Lioresal, 500 µg/mL) was administered via the pump. After 4 hours, the patient developed labored breathing and hemodynamic instability. We immediately removed baclofen from the ITB pump reservoir and transferred him to the ICU for observation. The next day he was discharged from the ICU without any problems. In light of this complication, we then administered 20 mL of baclofen (Lioresal 500 µg/mL) diluted with 40 mL of isotonic water into the reservoir of the pump. During the follow-up period, the spasticity decreased and the patient was discharged.

Two months later, the patient was admitted to our outpatient clinic for a second treatment of 20 mL of baclofen (Lioresal 500 µg/mL) diluted with 40 mL of isotonic water injected into the reservoir of the pump. Within minutes, the patient developed hypotonicity, hypertension, bradycardia, and respiratory difficulty followed by tonic-clonic seizures. He became unresponsive to both verbal and painful stimuli; there was no light reflex and his pupils were dilated. He was immediately intubated and taken to the ICU. He was breathing spontaneously, but his respiratory rate was 4 breaths per minute and weak. Intravenous access was rapidly established, and his cardiorespiratory status was monitored. His blood pressure was 73/40 mmHg, and his heart rate was 55 beats per minute. Blood gas analysis showed pH: 7.34, P_{CO_2} : 55.8, PO_2 : 66.8, lactate: 1.3, Na^+ : 137, K^+ : 4.02, base excess: 4.8, HCO_3^- : 30.7, and SO_2 : 91.3, and the patient was mechanically ventilated. Although we attempted to withdraw baclofen from the pump, we failed. This suggested a possible pump malfunction and an overdose of approximately 10,000 µg of baclofen since the pump's last fill. Thus, we inserted an indwelling spinal catheter in order to drain the excessive amount of baclofen from the spinal fluid.

One hour later, the patient again had a generalized seizure, and intravenous diphenylhydantoin treatment was administered. After the first 24 hours, noradrenalin infusion was started in order to keep the mean arterial blood pressure above 70 mmHg. When the heart rate dropped below 40 beats per minute, atropine was given; thus, we tried to keep the heart rate between 40 and 60 beats per minute. The patient was warmed, and we tried to keep the body temperature in the range of 35 to 37°C. During the first 24 hours, his neurological status was

unchanged. At the 31st hour, he was responding to painful stimuli with slow dystonic motor response, and at the 36th hour, his pupils began to respond to light. As the patient recovered, his spinal catheter was taken out and enteral tube feeding was begun. On the third day, noradrenalin infusion was stopped; the patient's GCS increased to 10/15, and his spontaneous respiration was adequate to allow him to be taken off the mechanic ventilator. By the 76th hour, the patient's neurological status returned to normal.

We performed a second surgery to replace the pump with a new one (Archimedes Implantable Constant-Flow Pump, filling volume 35 mL and flow rate 0.96 mL/24 h; Codman, Raynham, MA), and intraoperative radiological examination showed the tip of the pump catheter was placed at the level of T2. The postoperative period was uneventful, and the patient was discharged from the hospital with the advice to return for refilling of the pump. He is currently under our follow-up care. We did not encounter any neurological problems related to the second baclofen pump.

DISCUSSION

Although there have been several definitions of spasticity stated so far, the definition by Lance in 1980 has been most commonly used (4). Baclofen, a GABA-B agonist, became a part of the therapeutic arsenal in the 1960s. It has a weak capacity to cross the blood-brain barrier (BBB); therefore, oral doses must be high in cases of severe spasticity, which reduces its potential use in severely affected patients (5). Potentially life-threatening complications of ITB therapy include overdose and withdrawal syndrome. In addition, infections, wound dehiscence, seroma, cerebrospinal fluid leak, and mechanical problems related to the pump and catheter can occur, which can cause life-threatening complications (6), as seen in our patient. However, pump-related complications (ie, mechanical device failures) are said to be rare in currently available systems (7).

The malfunction of the drug pump allowed much of the administered baclofen to leak into the subarachnoid space at once and threatened our patient's life. The clinical picture of our patient was so serious that immediate intubation followed by mechanical ventilation was required. Furthermore, we needed to use inotropic drugs to keep the mean arterial blood pressure in the appropriate range. Baclofen overdose due to pump failure in our patient caused a generalized seizure; therefore, that an antiepileptic medication should be considered in the intensive management. Although baclofen pumps have port systems for withdrawal of the solution, a lumbar spinal catheter should be inserted immediately in severely toxic patients. To our best knowledge, our case of baclofen toxicity due to pump failure is the first one in which the patient showed signs of coma as well as a generalized seizure developing within minutes of the filling of the pump with baclofen.

CONCLUSION

Although ITB therapy is a very effective modality for the treatment of refractory spasticity, physicians must be aware of its serious complications. Although review of the literature showed that withdrawal syndromes are the most common cause of life-threatening complications of ITB, toxicity from overdose due to mechanical system malfunction must also be considered. Although safe, baclofen pumps are nevertheless mechanical devices that may malfunction. Baclofen pump filling is an important approach and should be performed in an advanced hospital with a suitable ICU and adequate emergency equipment because the clinical picture of the patient can abruptly worsen. Cerebrospinal fluid drainage is the most effective treatment in cases in which baclofen overdose is suspected.

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