CASE SERIES

BACLOFEN UNUSUAL RESPONSE IN SPINAL CORD INJURY PATIENTS

Sami Ullah, Maha Edrees, Ahmad Mushabbab Alhabtar*

Department of Rehabilitation Medicine, Rehabilitation Hospital, King Fahad Medical City, Riyadh, *King Faisal Medical City, Abha-Saudi Arabia

Spasticity after spinal cord injury is a major problem that can limit the effectiveness of rehabilitation programs. Oral baclofen is more frequently used in treating spasticity than other antispasmodic agents due to its proven overall efficacy. Herein, we are reporting two SCI patients who reported unusual response to baclofen. Case 1 (28-year-old male) his injury was classified as T3 AIS-A. Case 2 (36-year-old male) his injury was classified as T4 AIS-A. Both cases reported worsening of spasms with the initiation of baclofen and the rapid improvement upon discontinuing the medication. The effect was dose-dependent as reported by both of our patients. Our impression is a rebound spasm secondary to baclofen as evident by the severity of spasm and spasticity that were directly proportional to the baclofen dose. Awareness of this reversible side effect is essential for its management. Moreover, it might provide a clue to understanding the mechanism of action of baclofen**.**

Keywords: Spasticity; Spasms; Baclofen; Spinal Cord Injury; Rehabilitation; Case Series

Citation: Samiullah, Edrees M, Alhabtar AM. Baclofen unusual response in spinal cord injury patients. J Ayub Med Coll Abbottabad 2019;31(2):269–71.

INTRODUCTION

Spasticity after spinal cord injury (SCI) is a major problem that can limit the effectiveness of rehabilitation programs.[1] It negatively impacts patients, causing different physical impairment (e.g., pain, pressure sores, contractures), limitation of activities, dependency on caregivers, restricted participation in family and social life and decreased the overall quality of life.[2,3]

Drugs used to treat spasticity are tailored to each patient's specific needs.[4] Baclofen, tizanidine, dantrolene, and diazepam are commonly used drugs, which have different modes of action with the common aim of reducing muscle tone and spasms.[5] Along with rehabilitation program, oral or intrathecal baclofen is currently used for the treatment of spasticity after a Spinal Cord Injury (SCI)[6] and oral baclofen is more frequently used in treating spasticity than other antispasmodic agents[7] due to its proven overall efficacy. Baclofen is a GABA-agonist causing hyperpolarization of motor horn cells by selectively binding to presynaptic GABA-B receptors[8]. As a result, it decreases the hyperactivity of muscle stretch reflexes, clonus and cutaneous reflexes that elicit muscle spasms.[9] Baclofen is mainly water soluble and so does not readily cross the blood-brain barrier.[10] Due to this reason, high doses may be required to treat spasticity effectively, however intolerable side-effects[11] may occur at higher doses including hypotonia, nausea, vomiting, and lethargy[6].

In Saudi Arabia, spinal cord injury rate is mainly due to motor vehicle accidents 79.2%.[12] The majority of SCI patients are young adults[13] with a bulk of patients suffering from spasticity

Herein, we are reporting two cases from one of the largest hospitals in Saudi Arabia with a well-established inpatient spinal cord injury rehabilitation unit.

CASE-1

A 28-year-old male sustained traumatic spinal cord injury secondary to a fall in 2013. He had received inpatient rehabilitation in 2 different hospitals and was referred to Rehabilitation Hospital at King Fahad Medical City (KFMC). According to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), his injury was classified as T3 AIS-A. He had spasticity in his lower limbs with grade 2 on Modified Ashworth Scale (MAS) in his bilateral hip adductors, quadriceps, gastrocnemius and soleus muscles. He had received botulinum toxin injections for his lower limb spasticity and was on baclofen 25mg TID.

He reported improvement of his spasticity and decreased frequency of spasms after stopping baclofen. At that time, it was assumed that this might be due to poor compliance or lack of understanding of the potential triggers for spasms and spasticity. Consequently, he was provided patient education with baclofen 25 mg TID and asked to continue medication until next follow-up.

On his third follow-up visit, he reported that on continuous treatment with baclofen there is little improvement of his spasticity and frequency of spasms and his symptoms were considerably

worsened. However as soon as he discontinued the drug, he felt much better. On evaluation, there were no potential triggers on history and examination. So, baclofen was gradually discontinued with the tapering of the dose in two weeks. We discussed other options for treatment, and the patient opted for botulinum toxin (A) injections for management of his spasticity.

CASE-2

A36-year-old male, known to have insulin dependent diabetes mellitus and Hypertension on treatment (Insulin aspart. and Insulin glargine, Lisinopril). He sustained a traumatic spinal cord injury secondary to road traffic accident due to a hypoglycaemic episode, which resulted in a T4-5 fracture. He underwent surgical decompression and fixation of his thoracic spine. He had undergone multiple inpatient rehabilitation and received stem cell transplantation abroad without improvement. The patient was s paraplegic and according to the ISNCSCI classification, his injury was classified as T4 AIS-A. He suffered from a chronic right ischial pressure ulcer (grade 4) with osteomyelitis. The patient was admitted to KFMC for pressure ulcer and rehabilitation management. Upon his admission, he was found to have hypertonia with spasticity of grade 2 according to the MAS in the hip adductors, hamstring, gastrocnemius and soleus muscles bilaterally. He was treated with oral baclofen (25 mg) and a 12-week course of antibiotics and vacuum-assisted closure (VAC) therapy for his pressure ulcer. The patient was discharged home, with baclofen 25mg TID, orally, for his spasms and asked to follow-up in the spine rehabilitation clinic at KFMC. During his follow up appointment, his pressure ulcer had improved significantly with no evidence of infection both clinically and from a laboratory report. His diabetes and hypertension were well controlled with medication. Moreover, the patient reported worsening of his spasms with baclofen. Interestingly when he stopped his baclofen, he noticed a significant improvement in spasms. His spasticity was now around grade 1 in the hip adductors, hamstring, gastrocnemius and soleus muscles bilaterally. Thus, baclofen was discontinued, and we planned to monitor the spasticity.

DISCUSSION

Spasticity is commonly described as velocity dependent resistance in a passive movement that is associated with spasms and clonus.[14–16] There are multiple causes for spasticity and spasms, including traumatic spinal cord injury, with several aggravating factors such as skin ulcers, infections, renal lithiasis, constipation, pain or discomfort and sudden discontinuation of antispasticity drugs.[17,18] Various pharmacological and non-pharmacological treatment modalities are used to treat such cases.[19] Moreover, there are many different anti-spastic medications with varying side effects with baclofen being one of the most commonly used.[17] Due to the side effects and dose limitations of the medications, other forms of treatment are also needed. Botulinum toxin (Botox) injection is used for focal spasticity whereas Intrathecal baclofen pump is used in severe spasticity.[17,19] Management of spasticity is generally customized to patients' needs and a combination of treatment modalities is usually required.

It is considered as a muscle relaxant mainly used in spinal cord injuries and multiple sclerosis with analgesic affects.[20–22] Upon extensive literature review, there was no evidence of rebound spasms secondary to baclofen use. Ryan and Blumenthal have reported a similar case of dyskinesia as a side effect upon baclofen treatment.[23] They attributed it to the dopamine receptor hypersensitivity and imbalance that occurs as a consequence.[23] Unlike our cases, their patient had a history of alcohol abuse, basal ganglia stroke and concomitant use of phenytoin, which could have had a role to his dyskinesia.

In another similar case, Niehaus, *et al*., have reported about acute dyskinesia due to baclofen toxicity.[24] Their patient had a change in mental status and an underlying chronic kidney disease and was on zolpidem. In comparison our cases did not have any underlying renal disease and were not on central nervous system depressants. Additionally, there were no contributing factors for the increase in spasms such as infections including urinary tract infection, renal stones, constipation, pain, acute or chronic brain insult. There was, however, history of hypertension and diabetes in one of our cases without renal involvement. The patient was compliant with his medication and both his co-morbidities were under control. Also, our second patient has a chronic pressure ulcer that was being managed by our medical team and he improved without complications with time. However, his reported worsening spasticity after commencing oral baclofen was consistent on many occasions which were far apart from each other.

It is worth mentioning that this had recurred even while he was being managed or his pressure ulcer and osteomyelitis. However, as his ulcer and osteomyelitis were under control with no underlying infection, it was least likely possible that these could trigger his spasms.

Both of our patients noticed worsening of spasms with the initiation of baclofen. The effect

was dose-dependent as reported by both of our patients.

Our impression is a rebound spasm secondary to baclofen as evident by the severity of spasm and spasticity that were directly proportional to the baclofen dose and the rapid improvement upon discontinuing the medication. Although the mechanism of such an effect is unknown, other factors including renal failure and cerebral insult might contribute to such side effects as reported by the mentioned above case reports[23,24] which, however, is not applicable to our cases.

Awareness of this reversible side effect is essential for its management. Moreover, it might provide a clue to understanding the mechanism of action of baclofen. A closer look by the manufacturers of this drug on these effects as potential adverse drug reactions should be identified and further research is needed in this direction as these are not published in their investigator brochure.

AUTHORS' CONTRIBUTION

SU: Conceptualization, literature search, write-up, proof reading. MA: write-up, proof reading. AMA: Conceptualization, literature search, proof reading.

REFERENCES

1. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine (Phila Pa 1976) 2001;26(24 Suppl):S146–60.
2. Brainin M, Norrving B, Sunnerhagen KS, Goldstein LB, Cramer SC, Donnan GA, *et al*. Poststroke chronic disease management: towards improved identification and interventions for poststroke spasticity-related complications. Int J Stroke 2011;6(1):42–6.
3. Ryu JS, Lee JW, Lee SI, Chun MH. Factors predictive of spasticity and their effects on motor recovery and functional outcomes in stroke patients. Top Stroke Rehabil 2010;17(5):380–8.
4. Ertzgaard P, Campo C, Calabrese A. Efficacy and safety of oral baclofen in the management of spasticity: A rationale for intrathecal baclofen. J Rehabil Med 2017;49(3):193–203.
5. Chang E, Ghosh N, Yanni D, Lee S, Alexandru D, Mozaffar T. A review of spasticity treatments: pharmacological and interventional approaches. Crit Rev Phys Rehabil Med 2013;25(1-2):11–22.
6. Santamato A, Panza F, Ranieri M, Amouruso MT, Amoruso L, Frisardi V, *et al*. Effect of intrathecal baclofen, botulinum toxin type A and a rehabilitation programme on locomotor function after spinal cord injury: a case report. J Rehabil Med 2010;42(9):891–4.
7. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler 2004;10(5):589–95.
8. Meythaler JM, Guin-Renfroe S, Law C, Grabb P, Hadley MN. Continuously infused intrathecal baclofen over 12 months for spastic hypertonia in adolescents' adults with cerebral palsy. Arch Phys Med Rehabil 2001;82(2):155–61.
9. Campbell SK, Almeida GL, Penn RD, Corcos DM. The effects of intrathecally administered baclofen on function in patients with spasticity. Phys Ther 1995;75(5):352–62.
10. Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: a review. J Pharm Pharm Sci 2003;6(2):252–73.
11. Jose de A, Luciano P, Vicente V, Juan Marcos AS, Gustavo FC. Role of catheter's position for final results in intrathecal drug delivery. Analysis based on csf dynamics and specific drugs profiles. Korean J Pain 2013;26(4):336–46.
12. Ansari S, Akhdar F, Mandoorah M, Moutaery K. Causes and effects of road traffic accidents in Saudi Arabia. Public Health 2000;114(1):37–9.
13. Alshahri SS, Cripps RA, Lee BB, Al-Jadid MS. Traumatic spinal cord injury in Saudi Arabia: an epidemiological estimate from Riyadh. Spinal Cord 2012;50(12):882–4.
14. Thilmann A, Fellows SJ, Garms E. The mechanism of spastic muscle hypertonus. Variation in reflex gain over the time course of spasticity. Brain 1991;114(Pt 1A):233–44.
15. Dressler D, Bhidayasiri R, Bohlega S, Chana P, Chien HF, Chung TM, *et al*. Defining spasticity: a new approach considering current movement disorders terminology and botulinum toxin therapy. J Neurol 2018;265(4):856–62.
16. Elbasiouny S, Moroz D, Bakr MM, Mushahwar VK. Management of Spasticity After Spinal Cord Injury: Current Techniques and Future Directions. Neurorehabil Neural Repair 2009;24(1):23–33.
17. Graham LA. Management of spasticity revisited. Age Ageing 2013;42(4):435–441.
18. Nair KP, Marsden J. The management of spasticity in adults. BMJ 2014;349:g4737.
19. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: Physiology, assessment and treatment. Brain Inj 2013;27(10):1093–105.
20. Milanov I. Mechanisms of baclofen action on spasticity. Acta Neurol Scand 2009;85(5):305–10.
21. Watanabe TK. Role of Oral Medications in Spasticity Management. PM R 2009;1(9):839–41.
22. Pérez-Arredondo A, Cázares-Ramírez E, Carrillo-Mora P, Martínez-Vargas M, Cárdenas-Rodríguez N, Coballase-Urrutia E, *et al*. Baclofen in the Therapeutic of Sequele of Traumatic Brain Injury: Spasticity. Clin Neuropharmacol 2016;39(6):311–9.
23. Ryan DM, Blumenthal FS. Baclofen-induced dyskinesia. Arch Phys Med Rehabil 1993;74(7):766–7.
24. Niehaus MT, Elliott NC, Katz KD. Baclofen Toxicity Causing Acute, Reversible Dyskinesia. J Med Toxicol 2016;12(4):406–7.

Submitted: 11 May, 2018	*Revised: --*	*Accepted: 30 December, 2018*

Address for Correspondence:

Dr.Sami Ullah, Department of Rehabilitation Medicine, Rehabilitation Hospital, King Fahad Medical City, Riyadh-Saudi Arabia

Tel: +966-50-7175984

Email: drsamipmr@gmail.com