Bradycardia Related to Administration of Low Dose Intrathecal Baclofen

Düşük Doz İntratekal Baklofen Uygulamasına Bağlı Bradikardi

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ABSTRACT

We presented an unusual tetraplegic case with sinus bradycardia after intrathecal baclofen therapy (ITB). It was determined after lower doses of ITB administration, and the suspicion of overdosing or withdrawal syndrome which were the main risks of ITB came out. , In this case presentation, we investigated the causes of this bradycardia with the review of present literature. *(J PMR Sci 2010;13:31-3)*

Keywords: Intrathecal baclofen, bradycardia, spinal cord injury

ÖZET

İntratekal baklofen tedavisi (ITB) sonrası sinüs bradikardisi olan alışılmadık bir tetraplejik vakayı sunduk. Bu, düşük doz ITB uygulaması sonrası tanımlandı ve aşırı doz veya çekilme sendromu şüphesi doğdu. Bu vaka sunumunda, mevcut literatürler derlenerek bu bradikardinin nedenlerini araştırdık. *(FTR Bil Der 2010;13:31-3)*

Anahtar kelimeler: İntratekal baklofen, bradikardi, spinal kord hasarı

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Introduction

Spasticity is an important challenge in community-dwelling patients with spinal cord injury (SCI). It is the second most reported complication in SCI patients (40%) after urinary tract infections (1) and is characterized by hyperactive stretch reflexes and increased muscle tone.

Baclofen [4-amino-3 (4-chlorophenyl) butanoic acid] is one of the main drugs used in spasticity with spinal cord origin. It is a derivative of the inhibitory neurotransmitter γ aminobutyric acid (GABA). It principally acts on the $GABA_B$ receptor at the spinal level and inhibits the segmental polysynaptic spinal reflex pathways. The recommended maximum dosage is 80 mg per day although higher dose prescription is not uncommon. The most common side effect of Baclofen is sedation whereas overdosage may cause a wide spectrum of symptoms such as tachycardia, hypertension, bradycardia, seizure, coma, delirium and death. Because of its passage to blood-brain barrier is to a limited extend, intratechal baclofen treatment (ITB) is a widely used treatment alternative. Intrathecal administration of baclofen acts directly at the receptor sites in the spinal cord with greater therapeutic efficacy, smaller drug doses, and thus less systemic toxicity (2). Although the incidence of adverse effects range from 10-75%, the majority of them are generally dose related, reversible and not severe (3). The most common complications were muscle weakness, somnolence, catheter malfunction, and surgery complications.

In the literature, there is limited knowledge about cardiac rhythm disorders due to ITB therapy. In this article, we present an unusual case with sinus bradycardia after ITB therapy in a patient with spinal cord injury.

Case

A 26-year-old man with a traumatic spinal cord injury was admitted to our outpatient clinic. He had C5 tetraplegia ASIA-A because of a car accident 4 years ago. His major complaint was severe painful spasms on his lower extremities.

His neurologic examination revealed the last normal sensory level to be C6 with 3 levels of partial preservation. Strength was 5/5 in biceps and 2/5 in the wrist extensors and triceps bilaterally. There was no muscle power at his other key muscles. Tone was 2/4 (according to Modified Aschworth Scale) in the lower extremities mainly at abductors and knee extensors in the absence of a spasm, but 4/4 during a spasm. Spasms were causing severe pain and might be provoked with any superficial stimulation. Reflexes were hyperactive and there were achilles and patellar clonus. There was no pressure sore, and his bladder and bowel management had been provided successfully. An absolute grade of heterotopic ossification which limited his hip movements 50% at all directions were determined at both hips. He was taking 80mg Baclofen and 15mg Oxybutinin per day.

We increased the dose of oral baclofen up to 120 mg/day gradually and added tizanidin 12 mg/day. But we could not achieve significant reduction in spasticity. There were no adverse effects despite these high doses. Then, an intrathecal baclofen pump was placed 3 months ago. After that, painful spasms reduced quitely with a daily dose of 200 µg/day. He did not get any other drug for any reason. Interestingly, his resting heart rate decreased under 40/minute, although he had no history of any dysrhythmia or cardiac disorder at inpatient follow-ups. When we scanned the old records of the patient, we saw that his heart rate was 70-90/minute before the pump implementation. After cardiology consultation, echocardiography and 24-hour holter monitoring were performed to clarify the etiology of bradycardia. The maximal heart rate was 81 bpm and the minimal heart rate 36 bpm. His mean heart rate was 46 /minute and bradycardia was seen in day and night time. Because all holter records showed sinus rhythm and normal echocardiographic signs were observed, cardiology specialist did not suggest any pathology requiring any treatment. So, we thought that this cardiac rhythm disorder might be because of ITB administration. Then, we checked the ITB pump out, but there was no problem with the system. After all, we reduced daily dose of intrathecal dose to 125 µg/day gradually. Then, resting heart rate increased to 60 bpm at that dosage, when lower extremity spasticity level increased in physical examination.

Discussion

ITB therapy is effective for patients with especially severe spasticity of spinal origin, particularly for them who are not sufficiently managed by oral medications. Reduced spasticity and pain, and increased mobility are benefits of ITB therapy, however there are some rare and mainly transient complications with it. Most patients can adequately maintain with baclofen infusion on 300-800 µg/day. Armstrong et al reported some central side effects including hypotension and bradycardia were seen in some children who received continuous intrathecal baclofen infusion for spasticity of cerebral origin (4). It was reported that the action of baclofen at the brainstem level could cause dangerous reductions in heart rate, when ≥2000 µg intrathecal baclofen doses were used (5).

There is a case report in the literature about bradycardia that was observed after the first administration of 5 mg oral baclofen (6). Our case with tetraplegia have been received inpatient rehabilitation services at many times and used oral high dose baclofen for spasticity without any heart rhythm disorder. Because sinus bradycardia was determined after lower doses of ITB administration (125-200 µg/day), the suspicion of overdosing or withdrawal syndrome which were the main risks of intrathecal baclofen infusion came out.

In addition to the general risks of general anesthesia of a surgical procedure, the risks of spinal fluid leakage can be observed with implantation of the ITB pump. The catheter can become kinked or fractured. An unexpected escalation in dose requirement suggests a catheter complication. To clarify the probability of a kink, a disconnection or a dislodgment of pump-catheter system in our case, we made X-ray examination together with a radiologist and a neurosurgeon. Then, we could not observe any mechanic disorder.

Sedation or somnolence, excessive weakness, vertigo, diabetes insipidus, delirium and psychological disturbances are dose related and reversible adverse effects (3,7,8). Overdosage of ITB can also cause rostral progression of hypotonia, respiratory depression, coma, and occasionally seizures, and improve with cerebrospinal fluid subtraction of 30-50 ml or using phystostigmine. Perry et al reported some autonomic disturbances like bradycardia or tachycardia, hypotension or hypertension, and miosis or mydriasis due to oral baclofen overdose (9). They generally arises from drug test doses or human error during refill and programming of the pump. Because of this, we interrogated the pump status using Medtronic programmer. To exclude drug leakage, we calculated the totally consumed dosage since the date of last pump refilling, and compared the dosage in the pump seen with Medtronic programmer with resorvoir drug which was emptied with the needle.

As a result of a problem with the delivery system, withdrawal syndrome with symptoms like seizures, hyperthermia, exaggerated rebound spasticity, hallucinations, labile blood pressure or hypotension, rhabdomyolysis, hepatic and renal failure, coagulation disorders with disseminated intravascular coagulation, coma, and sometimes death can occur within 24-48 hours. This condition generally improve following readministration of oral baclofen at maximal doses (120 mg), intravenous diazepam, and intensive care symptomatic treatment. Baclofen bolus injection in the lateral access of the pump is possible.

Our case did not take part in a such poor condition. On the other hand, there was no problem with the delivery system. He was pleased with ITB therapy, because it had set free him from severe spasticity. Even, he did not feel any health discomfort.

The majority of cardiovascular and respiratory afferents relay to the central nervous system via the vagus and glossopharyngeal nerves and terminate in the nucleus tractus solitarii which is richly innervated from regions of the CNS concerned with cardiorespiratory control, and contains a high density of GABA containing nerve terminals (10). Thus, Monassier et al investigated the effects of baclofen on cardiovascular responses to stress in humans, and demonstrated a reduction in tachycardic response to mental stress test (11).

Despite reductions in serum drug concentrations to negligible amounts, cardiac arrhytmias can occur. Because apparent elimination rate of baclofen is much slower from nervous tissue than serum. So, The occurrence of arrhythmias does not correlate with baclofen concentrations (12). Our case also showed asymptomatic sinus bradycardia, after using intrathecal baclofen administration in a therapeutic dose range. If it was symptomatic, atropine could be a drug choice for bradycardia.

Since the bradycardia does not exceed the benefits of baclofen for patients with spinal spasticity, the benefit /risk assessment is favourable. To achieve the optimum balance between reduction in spasticity and maintenance of normal heart rate values, the adjusting of the baclofen dose is necessary.

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