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Case Report

Treatment of spasticity in a spinal cord-injured patient with intrathecal morphine due to intrathecal baclofen tolerance – a case report and review of literature

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Study design: Case report.
Objective: To report treatment of spasticity in a spinal cord-injured person with intrathecal morphine after the person developed tolerance to intrathecal baclofen.
Method: Spasticity in a 36-year-old man with T6 complete paraplegia was treated with increasing doses of intrathecal baclofen. When he developed tolerance to intrathecal baclofen, he was given continuous infusion of morphine intrathecally.
Setting: Regional Spinal Injuries Centre, UK.
Results: Spasticity was adequately controlled by intrathecal morphine.
Conclusion: In spinal cord-injured patients with severe spasticity, who become tolerant to intrathecal baclofen, treatment with intrathecal morphine may be useful.
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Keywords: intrathecal baclofen; intrathecal morphine; spasticity; tolerance

Introduction

Spasticity is a common complication of spinal cord injury resulting from hyperexcitability of stretch reflexes in a patient with upper motor neuron lesion.[1] Muscle spasm and increased tone may disturb sitting balance, interfere with self-care activities; endanger transfers in those who have a complete spinal cord injury.[1] It is often necessary to treat spasticity when it interferes with balance, mobility functional independence and activities of daily living. Baclofen (beta4 chlorophenyl gamma-amino butyric-acid) is commonly considered the treatment of choice for control of spasticity after spinal cord injury among other commonly prescribed oral medications. Orally administered baclofen may become ineffective in severe spasticity because of limitation of the dosage by systemic side effects and failure to reach the site of action at the spinal cord level in sufficient concentration. Continuous intrathecal infusion of baclofen has been shown to be a safe and effective treatment for severe spasticity of spinal cord origin and has become increasingly accepted.[2] Nevertheless, concern for baclofen tolerance remains an issue.[3] Tolerance is defined as a phenomenon manifested by an escalation of the dose required producing a previously obtained effect or by the decrement of the effect produced by a given dose of the drug.[3] Baclofen is an agonist of gamma-amino-butyric-acid-B (GABA-B) receptors, which are very superficial in the spinal cord.[3] A theory as to why tolerance develops for drugs, which exert their physiologic effects by interaction with specific receptors, is that repeated administration of the agonist causes either a reduction in the receptor number or an uncoupling of the receptor to effector molecules. This results either way in an increase in the concentration of a given agent necessary to achieve the functional occupancy in order to evoke a given effect.[3]

When spasticity is refractory to oral agents, it may be treated effectively with chronic intrathecal infusion of baclofen into the cerebrospinal fluid.[4] Continuous infusion of morphine into the cerebrospinal fluid has also been used to treat spasticity.[4] A primary site of action of spinal epidural or intrathecal morphine is in the neuron pool of the dorsal horn.[5] Morphine by systemic or spinal administration is receptor specific and affects primarily the multisynaptic reflexes associated with A delta or C fibre stimulation or little or no effect on the monosynaptic segmental reflex.[5] Hence in addition to blocking afferent pain transmission, the reflex arc contributing to spasticity might also be inhibited.[5]

We report a spinal cord-injured patient with marked spasticity who was treated with intrathecal morphine to

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alleviate the spasticity, since he had developed tolerance to intrathecal baclofen.

Case report

A 36-year-old gentleman sustained T6 paraplegia (ASIA-B) in a road traffic accident. He worked as a music teacher. About 12 years after he had sustained spinal cord injury, he complained of a numbness and dysesthesia of both hands. MRI of the spinal cord was performed, which showed a syrinx extending from C3 to T10. The neurological symptoms progressively became worse and a repeat MRI showed progressive expansion of the syrinx. He was admitted to the Spinal Unit for a syringopleural tube drainage. Preoperatively his neurology was sensory level of T6 with patchy loss of sensation over C4–C8 over both arms, right arm being involved more than the left. He had lost significant power of his handgrip. The surgical procedure of syringopleural shunt was performed satisfactorily on 21/01/00. Postoperative MRI scan of spinal cord showed the syrinx in a collapsed state. He had excessive overwhelming refractory spasticity of the trunk and limbs (Ashworth grade-4), which interfered in his activities of daily living and also affected the sitting balance on the wheel chair. He had tried almost all modalities to reduce the spasms including physical measures without meaningful benefits. He was started on oral baclofen, which progressively had to be increased to control the spasms. Despite the above measures and with maximum tolerable baclofen dose, his spasticity remained a major problem.

Finally, it was decided that the patient would benefit from the baclofen pump implant. A programmable synchromed Medtronic pump with access port (model 8627 EL) was implanted for chronic infusion of baclofen solution intrathecally. The surgery of implantation of programmable pump for intrathecal infusion of baclofen was performed on 14/4/00. The patient was given initially a bolus dose of 500 μg and a maintenance dose of 250 μg of baclofen by simple continuous infusion. All oral antispastic medications for spasticity were tapered and subsequently stopped. The dose of intrathecal baclofen dose was increased to 300 μg within 48 h and the spasms were brought under control. (Ashworth grade-2 to Ashworth grade-1). He was discharged within 2 weeks of surgery. The intrathecal baclofen dose subsequently had to be increased to bring the spasms under control.

Within 18 months after the implantation of the intrathecal baclofen pump, he continued to suffer with manifestations of overwhelming spasticity. Over a time period of 19 months, the intrathecal baclofen dose to control his spasticity rose from 250 to 1600 μg/day and was ultimately ineffective at that dose. We suspected baclofen tolerance. Our detailed clinical examination excluded problems with his neuropathic bowels, bladder or skin. Additionally, his blood tests and intravenous pyelographic profile were normal. Hence, X-rays for pump rotor movements and contrast dye injection into the side port and X-ray screening and a trial of intrathecal morphine were performed. These tests confirmed normal functioning of the pump rotors and patency of the tubing.

On 18/10/01, the Medtronic pump was emptied and refilled with intrathecal additive-free morphine sulphate. The dose, which was started, was 100 μg/day. The patient felt much better and had relief of spasms. The dose of intrathecal morphine was increased to 150 μg/day. Meanwhile the oral baclofen, which had to be started, was tapered off and stopped over a week. On 29/01/02, the patient came in for a refill of intrathecal morphine and the dose was maintained at 150 μg/day. On 02/02/02, the patient came in as a self-referral with moderate spasms and the dose was further increased to 185 μg/day of intrathecal morphine. On 29/7/02 his dose was increased to 300 μg/day and since then and has marked improvement in spasm control. He resumed his employment. The present dose of intrathecal morphine is 300 μg/day.

Discussion

Spasms and spasticity are serious complications for many patients with spinal cord injury.[6] Both indicate an imbalance in the mechanisms that regulate reflex motor activity at the spinal cord level.[6] By definition, spasticity is a state of sustained increased muscle contractility. It is a symptom complex characterized by hyperactive tendon reflexes, hyperactive muscle stretch reflexes, abnormal spinal reflexes and increased resistance to passive movement.[6] Standard treatment of spasticity includes physical therapy, antispastic agents and surgical lengthening of affected muscles or tendons. Microneurosurgical procedures have been tried to interrupt the spinal reflex arc or to reduce the afferent input to the dorsal horn, but with incomplete results.[6] Therefore, pharmacological management of spasticity has gathered interest in recent years. Baclofen is the agent that is used most often and is the drug of choice of spinal forms of spasticity.[6]

The exact mechanism of action is not fully understood. It is believed that baclofen acts primarily at the level of the spinal cord by binding to GABA receptors located at the superficial layer of the dorsal grey matter. Studies by Kroin *et al*[7] have conducted studies in animals and have shown that intrathecal baclofen downregulates GABA receptors in the rat substantia gelatinosa – and claim similar effects can occur in human beings.[7] Oral baclofen although a good drug for treatment of spinal cord injury-related spasticity has its limitations. Only a minute portion of the drug crossed the blood–brain barrier. Hence, intrathecal baclofen has been shown to offer many more advantages over oral administration.[6] High local concentration can be achieved at the spinal cord with small dosages considerably reducing the concentration of the drug to which the brain is exposed.[6] Nevertheless, a concern over intrathecal baclofen is whether patients will develop tolerance to the drug.[3]

Penn and Kroin[8] first proposed intrathecal baclofen therapy for spinal spasticity. Since then various studies have been done to substantiate this.[3–10] The safety and efficacy of intrathecal baclofen have been confirmed by Abel and Smith.[11] Apart from improvement of spasticity of the lower limbs studies by Burns and meythaler[12] have used intrathecal baclofen upper extremity spasticity in tetraplegic patients. Penn and Kroin[8] and Ankman *et al*[3] were the first authors again who pointed out the problem of tolerance. There is sparse material in relation to intrathecal baclofen tolerance, which prompted us to report this case and conduct review of the literature.

In the study by Ankman *et al*,[3] the required baclofen dose needed to keep spasticity at an acceptable level was highlighted. They concluded that in spinal cord-injured patients; there is no difference in treatment of spasticity in complete/incomplete injured patients with intrathecal baclofen as regard to dosage over time. They suggest tolerance *per se* should not dissuade one from choosing intrathecal baclofen for treatment of spasticity.[3]

In the study by Penn and Kroin[13] where spinal cord-injured patients with spasticity were treated with intrathecal baclofen, they have raised the issue when gradual increase of doses of intrathecal baclofen and continued escalation of the doses could lead to gradual tolerance. They have suggested that longer trial is needed. Penn and Kroin[13] have reported morphine sulphate given intrathecally to reduce spasticity. Erickson *et al*[5] has highlighted the same in his study.

Penn and Kroin[13] had treated two patients apart from their study group by infusion of morphine sulphate and found similar results with low continuous doses. Penn and Kroin[13] have raised the possibility of switching medicines to use intrathecal morphine if significant tolerance to baclofen develops.

In the study put forth by Erickson *et al*,[14] patients with both spinal and cerebral origin spasticity were treated with epidural morphine. They have reported that intrathecal morphine delivered by a continuous flow pump or by injection into the reservoir can effectively control spasticity of the trunk and lower extremity in most patients.[14] However, in the same study Erickson *et al*[14] have pointed out that one patient developed tolerance to morphine sulphate.

The primary site of action of intrathecal morphine is in the neuron pool of the dorsal horn.[5] It has been found that morphine by systemic or spinal administration is receptor specific and primarily affects the multisynaptic reflexes associated with A delta or C fibre stimulation with little or no effect on the monosynaptic segmental reflex.[5] Therefore in addition to blocking afferent pain transmission, the reflex arc contributing to spasticity might also be inhibited by morphine.[5] In the study by Bloomfield *et al*,[15] morphine has been well proven to be successful in treating pain.

Erickson *et al*[5] used intrathecal morphine to treat spinal origin spasticity, but have put forth the concern whether drug tolerance will follow with subsequent increasing dosage and be concomitant potential for addiction. They have reported one patient among the four patients who were being treated developing tolerance to morphine.[5]

Here in our case report, a 36-year-old gentleman who was an incomplete spinal cord-injured patient (T6 ASIA-B) developed deteriorating neurological symptoms related to a syrinx 12 years after his injury and was subsequently treated surgically for the same. He had relief of his spasms with intrathecal baclofen in the form of functional improvement. In the study by Azouvi *et al*,[16] long-term efficacy and marked improvement of the functional independence was observed in the study group of patients who had spinal cord injury and were treated with intrathecal baclofen.

Our patient in this case report developed baclofen tolerance. Pump system failure was ruled out by checking rotor movement through X-ray examination of the pump. X-ray imaging and contrast injection through the access port proved normal patency of the tubing. There are reports where baclofen pump catheter failure has given rise to complications because of acute baclofen withdrawal, secondary to disconnection of the intra- and the extraspinal portions of the catheter-like neuroleptic malignant syndrome, hyperthermia and sepsis could occur.[17] Levin and Sperling[18] also have mentioned about complications associated with infusion pumps implanted for spasticity in his study.

In our patient after ruling out a pump failure and tubing-related problems, it was decided to change over to intrathecal morphine as studies shown by Penn and Kroin.[13] This case profile over a period confirmed that he required escalating intrathecal baclofen dosages without significant benefit with regard to relief of his spasticity, hence intrathecal morphine was considered. The result was that a low dose of morphine was enough to control the spasticity. On 18/10/01, the intrathecal morphine was started and at his last pump refill on 4/11/02, 13 months later, he remains on 300 μg/day The patient has reported an improvement in the functional outcome with resumption of his employment.

Conclusion

In treating patients with spasticity of spinal cord origin, if baclofen tolerance occurs with intrathecal baclofen therapy, trial with intrathecal morphine can help to overcome this specific and rare problem. However, trials with larger population on a long-term basis are required.

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