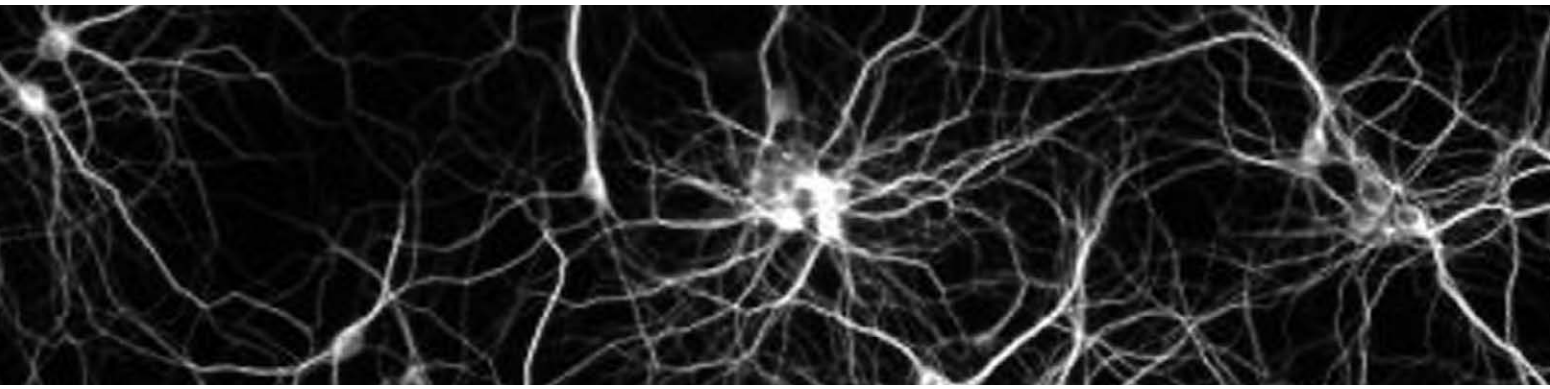

Anesthesiological approach to intrathecal baclofen overdose

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ABSTRACT – *Objectives:* We report two cases of intrathecal baclofen overdose, clinical course, and management. Our aim is to educate healthcare workers about possible choices for the management of intrathecal baclofen overdose. *Case description:* A 61-year-old patient with spastic tetraparesis and baclofen pump therapy was admitted to the intensive care unit due to neurological deterioration and respiratory depression. He required periodic increases in the dosage of intrathecal baclofen and antipsychotic drugs for baclofen psychosis. On admission, he was hemodynamically unstable, and laboratory results indicated inflammation and hyperglycemia. Second patient, a 29-year-old, with also spastic tetraparesis and baclofen pump therapy, was admitted to the intensive care unit after pump manipulation with neurological deterioration and bradycardia. Both patients fully recovered after symptomatic treatment and reduction of intrathecal baclofen delivery to a minimum. *Conclusion:* Being one of the few centers in Croatia in which implanting and managing patients with baclofen pump is done, we need to be prepared to solve the adverse effects of baclofen such as overdose, always having in mind there is no antidote for baclofen, and that there are no guidelines for the management.

Keywords: intrathecal baclofen, overdose, spine trauma

INTRODUCTION

Baclofen is a gamma-aminobutyric acid (GABA) derivative acting as a presynaptic and postsynaptic agonist of $GABA_B$ receptors (1,2,3,4). Since it relieves the spasticity, it is used to treat muscle spasms of cerebral and spinal origin caused by various neurological disorders, such as after brain injury (including posttraumatic brain injury and

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stroke), cerebral palsy, upper motor neuron syndrome, or by spinal cord disorders, such as spinal cord injury (4,5). Oral baclofen is mainly water-soluble and does not easily cross the blood-brain barrier so higher doses are needed of the same effect as intrathecal baclofen (3,5). The concept supporting intrathecal therapy is the delivery of baclofen directly to the site of action, the spinal cord, via a programmable pump implanted in the abdominal wall, which enables the delivery of smaller doses avoiding the systemic side effects. It is suggested that the tip of the intrathecal catheter should be placed at the T1–T2 level for spastic quadriplegia, the T6–T10 level for spastic diplegia, and in the midcervical region for dystonia (6). Intrathecal baclofen has been demonstrated to improve significantly daily activities, but it is not without complications (7). The most serious complication is overdose, usually caused by a malfunctioning pump, keeping in mind there is no antidote for baclofen and that there are no national guidelines for the management (3,6).

Being one of the few institutions in Croatia implanting baclofen pumps for spams caused by spinal trauma, we present here the clinical course, encountered problems, and management of two cases of intrathecal baclofen overdose.

CASE REPORT

PATIENT 1

In the 61-year-old male with spastic tetraparesis after cervical spine trauma and following surgery at the level C6-C7, the baclofen pump (*Syncromed II, Medtronic, Minneapolis, Minnesota, USA*) was implanted in August 2017, following a successful baclofen trial. Required dosage increase of intrathecal baclofen periodically since 2017 and since February 2021 in therapy with antidepressant because of baclofen psychosis.

He was admitted to the hospital in May 2022 with a progression of spasticity and psychotic elements (would not eat or drink). The psychiatrist adjusted the psychiatric therapy (olanzapine/haloperidol, diazepam, lorazepam). Following the evening psychiatric therapy, the next morning, the patient was admitted into the intensive care unit (ICU) due to deterioration of clinical state: Glasgow coma scale score 3, miosis, but breathing spontaneously. The patient was intubated and mechanically ventilated, and fluid therapy (crystalloids) with diuretics (furosemide) was initiated, while the baclofen pump infusion was decreased to a minimal flow (96mcg/day). Since the patient was hemodynamically unstable (blood pressure 80/40 mmHg), continuous vasopressor support was initiated (noradrenaline 6-15mcg/kg/h). Computed tomography (CT) of the brain showed no signs of ischemia or hemorrhage, but chest radiography showed signs of pneumonia.

Laboratory results indicated inflammation (CRP 196 mg/L normal range <5.0mg/L, neutrophils 7.27×109/L- normal rage 2.06-6.49x109/L, lymphocytes 0.73×109/L – normal range 1.19-3.35x109), and hyperglycemia of 19.7 mmol/L (4.4-6.4mmol/L).

After 19 hours of mechanical ventilation and supportive therapy, the patient fully recovered, with no neurological symptoms, and baclofen therapy was continued.

PATIENT 2

In the 29-year-old male patient with incomplete spastic tetraplegia after cervical spine trauma at level C4 and surgery, the baclofen pump (*Syncromed II, Medtronic, Minneapolis, Minnesota, USA*) was implanted in March 2019, following a successful baclofen trial. He was admitted to the hospital due to the suspected baclofen pump malfunction, but the malfunction was excluded with the CT.

On the day of admission to the ICU, the patient showed bradypnea (7 breaths/minute), bradycardia (40 beats/minute), sopor, and was only reactive to the pain. Therefore, the baclofen pump infusion was decreased to minimum flow (96 μg/day) and the flow modality was changed. The laboratory results were within normal ranges, except for the lymphocyte count (1.13×109/L normal range 1.19-3.35x109). Symptomatic therapy was administered (atropine boluses of 1 milligram), with fluid therapy (crystalloids) and diuretics (furosemide).

The patient was fully recovered after several hours. He was discharged from the ICU with no new neurological symptoms, and the baclofen therapy was continued.

DISCUSSION

Intrathecal baclofen, administered via baclofen pump, is delivered directly to the site of its action in the spinal cord, bypassing the blood-brain barrier entirely. Acting as presynaptic and postsynaptic agonists of $GABA_B$ receptors (1,2,3,4), intrathecal baclofen downregulates receptor sensitivity, so

there is a potential risk for tolerance over time. Despite the fact that the number of baclofen receptors is decreased, it is the baclofen that can cause suppression of neuronal activity (2).

Manifestations of a baclofen overdose include respiratory depression, diffuse hyporeflexia, diffuse hypotonia, coma, hypothermia, bradycardia/tachycardia, delirium, seizures, and cardiac arrhythmias (1,2,4,8). The deterioration can be rapid and may even require cardiopulmonary resuscitation (9).

The most common cause of overdose is malfunction of the pump in the majority of cases (90%). Mechanical flow problems are common, so it is important to confirm pump and catheter localization. Overdose can also occur as a result of iatrogenic mistake, by incorrect re-filling of the pump or by to high infusion rate (3,6).

Overdose could easily occur as a result of increased baclofen infusion rate, in order to mitigate aggravated spasticity caused by noxious stimuli. Namely, the noxious stimuli (i.e., urinary tract infections, constipation) increase the afferent input (incoming nerve message to the CNS) on the stretch reflex (10).

In our patients, we confirmed the correct position and functioning of the baclofen pump. Therefore, the possible cause of baclofen toxicity/overdose in the first patient could be the concomitant psychiatric therapy that acted as respiratory depressants. Also, we could stipulate that inflammation caused the alternation of pharmacodynamics and pharmacokinetics of baclofen, although it has not been investigated previously. In the second patient, we suspected that the overdose occurred due to the pump manipulation during re-filling.

Regardless of the cause of the baclofen overdose, the problem is that there is no antidote for baclofen. It has been shown that atropine and neostigmine administration, or the lumbar punction and cerebrospinal fluid drainage, along with supportive care (fluids, diuretic, mechanical ventilation) have been successful in sporadic cases (2,3,4).

The additional problem could pose the potential development of serious withdrawal symptoms after a baclofen overdose in patients who have been receiving baclofen chronically. Therefore, it is important to reinstate the baclofen administration under strict monitoring, once the overdose symptoms are gone (1).

CONCLUSION

Patient with intrathecal baclofen pump are at possible risk of serious adverse events, such as acute baclofen overdose. There is no antidote for baclofen, so the current therapeutic efforts for baclofen overdose are directed towards minimizing intrathecal delivery of baclofen and lowering the availability of baclofen for binding to receptors, with the concomitant employment of symptomatic therapy.

In the setting of no official guidelines for baclofen overdose, case reports such as this are a valuable source of therapy for the clinicians and a possible foundation for the guidelines development.

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