Physostigmine in the treatment of intrathecal baclofen overdose

Report of three cases

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The expanding use of intrathecal baclofen for spasticity has raised a concern about the treatment of overdose in these patients, since no specific baclofen antagonist is available. Since physostigmine has been reported to reverse the respiratory depression and somnolence due to opiates, the drug was tried for the treatment of baclofen overdose. In three cases, intravenous physostigmine (2 mg) completely reversed the respiratory depression and coma caused by boluses of 80 to 800 μg of lumbar intrathecal baclofen. Physostigmine, although not a specific antagonist, should provide increased safety for patients receiving intrathecal baclofen.

KEY WORDS • baclofen • physostigmine • respiratory depression

The intrathecal use of baclofen for severe spasticity is expanding. One major concern in its use has been that no antagonist exists, and thus there is no specific treatment for an inadvertent overdose. Physostigmine has been shown to rapidly reverse respiratory depression and somnolence due to opiate overdose. Since these are the two most serious effects of baclofen overdose, the value of physostigmine as an antidote was investigated. Experience in three cases suggests that it is an effective agent. These cases and a protocol for its use are presented.

Case Reports

Case 1
This 46-year-old man, who weighed 83 kg, received an 800-μg baclofen overdose through a lumbar subarachnoid catheter with its tip placed at L4–5. The patient suffered from severe spasticity caused by a spinal contusion 10 years previously. While waiting for an exchange pump after 14 months of successful continuous spinal infusion of baclofen, the patient learned to give himself injections through a subcutaneous infusion port connected to the spinal catheter. The overdose occurred from a single 800-μg bolus.

When he first arrived at the hospital, the patient was comatose, with a respiratory rate of 4 to 6 breaths/min. The patient had muscle flaccidity and was vomiting. There was no cardiovascular depression. Physostigmine (0.4 mg/ml) was given intravenously at a dose of 2 mg over a 2-minute period (total volume 5 ml). Within 2 minutes, the respiratory rate was normal (12 to 14 breaths/min) and the patient was awake. He fell asleep but was arousable for 30 minutes, then again lapsed into a coma. A second injection of 2 mg physostigmine was given and the patient woke up within 2 minutes. Muscle power returned and rigidity and spasticity increased. In the following hours, the respiratory rate remained normal (12 to 14 breaths/min) and the patient was arousable. Normal alertness slowly returned.

Case 2
This 29-year-old man, who weighed 76 kg, received an 80-μg baclofen overdose through a lumbar subarachnoid catheter with its tip placed at L4–5. The patient suffered from spinal spasticity caused by multiple sclerosis. This patient was very sensitive to intrathecal baclofen, and previous doses exceeding 20 μg had caused mild overdose symptoms.

Upon receiving the 80-μg bolus, the patient became drowsy and the respiratory rate decreased to 8 breaths/min. There was muscle weakness and vomiting. A single intravenous dose of 1 mg (2.5 ml of a 0.4-mg/ml...
solution) physostigmine restored the respiratory rate to normal (14 breaths/min) within 2 minutes. The patient was awake and his muscle strength returned. After 40 minutes, muscle power decreased again, but the patient remained awake with normal respiration. No additional physostigmine injections were given, and the patient recovered completely.

Case 3

This 36-year-old man, who weighed 90 kg, received a 150-μg baclofen overdose through a subarachnoid catheter with its tip placed at T-6. He suffered from severe right-sided spasticity due to head trauma several years before. Since his symptoms involved the upper and lower extremities, the catheter tip had been advanced to the midthoracic level rather than the usual lumbar level. Previous lumbar injection of up to 100 μg baclofen had not produced any signs of overdose. The 150-μg bolus was given via an implanted infusion pump at T-6.

Thirty minutes after receiving the baclofen bolus the patient was alert; however, at 90 minutes he was drowsy but arousable. He was connected to an apnea monitor. During the next hour it became increasingly difficult to arouse him. Three hours after receiving the bolus he was unresponsive to painful stimuli, his pupils were areflexic. Respiratory rate (8 to 20 breaths/min) was normal, as were blood pressure and heart rate. Physostigmine salicylate (Antilirium®), 1 mg, was diluted in 50 ml saline and delivered via an intravenous infusion pump at a rate of 0.1 mg/min. His condition gradually improved so that by 2 minutes he was spontaneously moving his left arm. The dose was reduced at 3 minutes as return of tone was noted in his right arm. After 5 minutes of infusion with a total dose of 0.34 mg, he exhibited return of bilateral spontaneous arm movement, he had facial grimacing when his affected right arm was passively moved, and his pupils returned to normal. With 8 minutes of physostigmine infusion, he was spontaneously opening his eyes and following simple commands. The infusion was discontinued at 10 minutes after infusion of a total of 0.44 mg (22 ml of 0.02 mg/ml solution). The patient was awake and alert, although he said he felt sleepy and his vision was blurry. It was particularly interesting that the muscle tone in his affected right side did not become abnormally high and he could use his arm and hand better. Ten hours after the bolus injection and 7 hours after the physostigmine infusion he was back to baseline status.

Discussion

Although physostigmine is not a specific antagonist to baclofen, it can reverse the main side effects associated with an intrathecal baclofen overdose. Clinically, physostigmine reversed the respiratory depression seen with large baclofen overdoses (up to 800 μg). In a sensitive patient, in whom an 80-μg bolus produced respiratory depression, a single physostigmine injection restored the respiratory rate to normal. Physostigmine was also effective in restoring alertness in these patients. The usual therapeutic dose of intrathecal baclofen given continuously using an implanted infusion pump ranges from 15 to 670 μg/day, depending on the symptoms of spasticity in each patient.

Our experience with physostigmine therapy for baclofen overdose is similar to results obtained in studies of opiate overdose. Weinstock, et al., found that physostigmine at 0.1 mg/kg antagonized the effect of high doses of systemic morphine in dogs, improving respiratory and alertness. Because of the short half-life of physostigmine in the central nervous system, a repeat injection after 30 minutes was sometimes required. When this technique was extended to patients receiving systemic morphine for post-surgical pain, it was found that 1 mg physostigmine administered intravenously restored respiration to normal and abolished somnolence for 40 to 60 minutes. Physostigmine delivered intravenously at 0.04 mg/kg has been used to treat heroin overdose. Addicts in a coma with respiratory depression regained consciousness and began breathing regularly within 10 minutes after physostigmine administration. The somnolence produced by epidural morphine in two patients was also successfully reversed by intravenous administration of 1 mg physostigmine.

Based on the present study, a protocol for treatment of intrathecal baclofen overdose is proposed. Physostigmine is prepared by diluting 4 mg of the commercial physostigmine salicylate solution (two ampules of 2 mg/2 ml in the United States) in a 100-ml bag of sterile saline for injection, yielding a concentration of approximately 0.04 mg/ml. This is placed in an intravenous infusion pump and dispensed at a flow rate of 5 ml/min (0.2 mg/min) for 5 to 10 minutes, yielding a total dose of 1 to 2 mg. If there is improvement in respiration and alertness, then repeat doses of 1 to 2 mg should be administered at 30- to 60-minute intervals to maintain adequate respiration and alertness. However, if respiratory depression persists after physostigmine injection, the patient must be intubated.

A major point emphasized by the present study is the caution that must be used in giving intrathecal boluses of drugs, such as baclofen, versus slow continuous infusion. Studies of intrathecal morphine have shown that significant cisternal levels are reached as early as 1 hour after a lumbar injection. Therefore, high-dose boluses of hydrophilic drugs, such as baclofen or morphine, can rapidly affect brain function. Although intrathecal baclofen has proved effective in treating spasticity of spinal origin, one reservation concerning its use has been the lack of an effective antagonist in cases of drug overdose. Physostigmine, by reversing the respiratory depression and somnolence caused by high doses of baclofen, should be a useful

* Antilirium supplied by Forest Pharmaceuticals Inc., St. Louis, Missouri.

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antidote. The exact mechanisms of how cholinergic potentiation restores respiratory rate and alertness are not clear. Recently, a specific baclofen antagonist of low potency has been described. Future work may lead to the development of more potent antagonists acting at the baclofen receptor. For the present, however, physostigmine does provide increased safety for patients receiving intrathecal baclofen.

References


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