Long-term intrathecal baclofen infusion for treatment of spasticity

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Seven patients with spasticity of spinal cord origin have been maintained for up to 2 years with continuous spinal intrathecal infusion of baclofen. Prior to treatment, all of the patients had severe rigidity in their lower limbs and most had frequent and extensive spontaneous spasms, all of which greatly interfered with their activities of daily living. Oral antispasmodic medications were ineffective or caused central side effects. The patients underwent implantation of a programmable drug pump connected to a lumbar subarachnoid catheter. Within days of beginning continuous intrathecal baclofen infusion, the muscle tone was reduced to normal levels and spasms were eliminated. Over the ensuing months, muscle tone remained normal, but short-duration spasms could be induced by some activities. The greatest benefits to the patients were improvement in activities of daily living and better sleep due to reduced spasms. The baclofen doses were increased over the first few months but then were stabilized or only increased slightly, with the maximum dose being 650 μg/day. The most serious complications were two drug overdoses which took several days to clear up and were due to malfunctions of an earlier pump model. Baclofen clearance from the cerebrospinal fluid occurs with a half-life of 5 hours. The most serious concern in maintaining patients indefinitely on intrathecal baclofen is whether drug tolerance will eventually occur.

KEY WORDS • baclofen • spasticity • intrathecal drug delivery

Severe spasticity and associated flexor and extensor spasms frequently cause pain and suffering in neurologically impaired patients. Oral medications have only slight modulating effects and are often poorly tolerated at the high doses necessary to bring the symptoms under partial control. Neurosurgeons, challenged by this clinical problem, have devised a number of operative procedures. At the turn of the century dorsal rhizotomies were employed, and then a range of alternative procedures such as myelotomies, anterior rhizotomies, and even cordectomies in extreme situations have been used.

An alternative to these destructive procedures is the selective application of medications to modify the abnormal drive on the motor neuron pools. With implanted drug pumps and catheters, this type of selective delivery of medication to the spinal cord has become practical. In early reports it was shown that segmental polysynaptic spinal reflex pathways in animals could be inhibited using intrathecal baclofen and that chronic intrathecal application of baclofen in patients with multiple sclerosis and spinal cord injury could reduce their severe spasticity. In this article, we report on the long-term effects of intrathecal spinal infusion of baclofen in seven patients who have been followed from 11 months to 2 years.

**Clinical Material and Methods**

The seven patients who were selected for implantation of a drug delivery system all had severe rigidity, and six of the seven had spontaneous spasms that significantly interfered with activities of daily living as well as sleep. Their age, sex, cause of spasticity, degree of mobility, and duration of treatment are given in Table 1. Oral medications, including baclofen and diazepam, had been of no value or had caused side effects. The patients had had an initial trial of intrathecal baclofen, 25 to 50 μg, given via a subcutaneous port attached to a catheter in the lumbar subarachnoid space. No central symptoms such as drowsiness, confusion, or generalized weakness were seen at these doses, and each patient had a reduction in tone to normal and cessation of spasms for 4 to 8 hours following the bolus.

After the successful bolus trial, the Medtronic drug delivery system* was implanted subcutaneously in the

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* Drug delivery system, Model 8601, manufactured by Medtronic, Inc., Minneapolis, Minnesota.
Clinical data on the seven patients in this series with spasticity

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<th>Case No.</th>
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Effect on Rigidity and Spasms

The rigidity in the lower extremities was reduced to normal tone in all the patients, and this has been maintained throughout the study (Fig. 1 left). In one patient (Case 5) who relied on her extensor tone to transfer (for example, from bed to chair) and take several steps, the baclofen dose was adjusted to a level that did not interfere with function during the day (8 μg over 12 hours). The dose was increased to a slightly higher level (12 μg over 12 hours) at night for greater relaxation, so she fluctuated from Ashworth grade 2.5 to 1.5 cyclically. Spasms were greatly reduced in the six patients who were symptomatic (Fig. 1 right). During the first 4 to 6 weeks no spasms could be induced, even by vigorous physical stimulation. After that, small short-duration spasms could be induced with such stimulation, but they did not interfere with daily activities or sleep and did not cause pain. After 20 months, one patient has had a mild increase in spasms but is able to work and continues to sleep well.

If baclofen was withdrawn, the rigidity gradually recurred over a 3- to 4-day period. This happened in one patient who did not return in time for a refill and in another whose dose was purposely reduced by half for several days as a trial.

Voluntary control in the lower extremities was absent or greatly impaired in our patients, so the effect of baclofen on motor control could not be reliably studied. In two patients, strong adductor spasms prior to intrathecal baclofen inhibited voluntary abduction. With baclofen infusion such movements could be performed. In Case 5, too high a level of baclofen (> 20 μg/day) led to weakness and loss of the ability to stand and transfer independently. Two patients, unable to ambulate because of spasms, are now able to walk with long leg braces and crutches, but not because of improved voluntary control. Rehabilitation, which had been abandoned in three patients because of rigidity and spasms, was begun again and three patients have returned to work. Bladder dysfunction has improved. Four patients with prior incontinence are no longer impaired, and one patient is able to catheterize herself, which had previously been impossible because of adductor spasms. Uniformly, the patients have been able to sleep better because of reduced spasms.

The dose of baclofen necessary to achieve these results has varied widely, from 15 to 650 μg/day (Fig. 2). During the first 3 to 4 months a gradual increase in dose was required in all patients except one (Case 5), who did not have spasms and did not need to have her

Results

Effect on Rigidity and Spasms

The rigidity in the lower extremities was reduced to normal tone in all the patients, and this has been maintained throughout the study (Fig. 1 left). In one
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Fig. 1. Graphs showing the reduction in rigidity (left) and spasms (right) in the lower extremities following intrathecal baclofen treatment. Left: Data are from five patients, shown by different symbols, who have been maintained on baclofen for 1 year or more. The patient who used her extensor tone for transfer, as from bed to chair, and for steps (Case 5) was excluded. Rigidity was evaluated by the Ashworth scale (see Table 2). Right: Same patients as illustrated left. Frequency of spasm scale: 0 = no spasms; 1 = mild spasms induced by stimulation; 2 = infrequent full spasms occurring less than once per hour; 3 = spasms occurring more than once per hour; and 4 = spasms occurring more than 10 times per hour.

tone reduced to normal. A gradual increase in dose, by 20% to 30%, was needed in two patients in the 2nd year of treatment. In only one case has the increased dose resulted in central side effects. The patient noted lightheadedness, mild weakness, and nausea at a dose of 700 µg/day, but when the rate was decreased by 10% the symptoms cleared. However, her spasticity was not quite as well controlled as during the initial 12 months of treatment. None of the other six patients had similar central side effects when given the drug continuously. Specifically, no drowsiness, confusion, or weakness was seen. However, during bolus administration, three patients reported mild lightheadedness for 30 to 60 minutes, and this mode of intermittent administration was discontinued.

Complications

The pump pocket had to be revised and enlarged in one patient because of erosion of the incision by the side of the pump. Two pumps were replaced with new ones. The first was taken out for bench testing because of a drug overdose, and the second was removed at 19 months because a "beep" occurred two or three times per day. The pump is programmed to beep when the battery is low or when a malfunction occurs. Both pumps appeared to be functioning properly when tested by the manufacturer. In two patients, several months after implantation the thin-walled catheter kinked as it came off the pump port, stopping the delivery of medication. The tubing was replaced with heavier Silastic material, which has been used in subsequent implants, and no other kinks have occurred. In one patient, a small nick had been made inadvertently in the catheter wall by the surgeon and had to be repaired. No infections occurred and the lumbar catheters functioned without obstruction. Small fluid collections developed around the pump in several patients immediately post-operatively, but they resolved spontaneously in 10 to 14 days.

Drug Overdose

Two serious drug overdoses occurred in patients who were receiving medication in the bolus-delay delivery mode. Engineering analysis revealed that the problem was due to a combination of design factors. The Medtronic device employs a rotary pump with two rollers that advance the fluid through the tubing. At two points in the rotor cycle, only one of the rollers presses against the tubing so the resistance is less. Because the reservoir is under high positive pressure, the pump can leak if the single roller is not providing enough pressure against the tube. In the bolus-delay mode the pump stops at random, and if only one roller is against the tubing and does not exert sufficient force a significant leak can occur. This mechanism of failure was discovered only after an x-ray film of the pump, taken when the overdose occurred, was analyzed and showed the roller in this position. Appropriate bench testing was then performed, and leaks were found in a few pumps. To find
the cause of the pump overdose, extensive open discussions between the clinical investigators and the engineering staff at Medtronic, Inc., were required.

Since most of the patients were on the continuous-delivery mode, they had no problem. The two patients who had overdoses wished to continue on the program and were restarted on a continuous dose using a maximum concentration of 500 µg/cc baclofen. No further overdoses have occurred. With the engineering problems identified, a new rotor tubing design program was created, and pumps now produced must pass bench tests requiring that leakage be less than 5 µl/hr in any position of the rotor. Currently, all patients are kept in the continuous-delivery mode, and if the pump is to be stopped for testing purposes the fluid is to be removed.

The two instances of pump overdose provided a unique opportunity to observe the effects of high-dose lumbar intrathecal baclofen. One patient received 1.5 to 2 mg over 3 hours and the other received 4 mg (Cases 6 and 7, respectively). Their clinical picture was similar, consisting of mild lightheadedness and weakness in the upper extremities which developed over 30 to 60 minutes, followed rapidly by drowsiness and then loss of consciousness. Both patients were brought to the hospital and were intubated for safety, although respiration had only slowed to 8 to 12 breaths/min. The remaining baclofen was removed from the pump reservoir. The patients were hypotonic and did not respond to deep pain; the pupils remained small but reactive, and blood pressure and heart rate were normal. Lumbar punctures were performed and the lumbar cerebrospinal fluid (CSF) had a drug concentration of 4.8 and 11.3 µg/ml for the two patients, respectively. Subsequent lumbar taps demonstrated that the half-life of baclofen is approximately 5 hours, so by 16 hours the level of baclofen was 0.3 and 1.3 µg/ml, respectively. The patients remained in coma for 24 to 36 hours and then gradually became less obtunded and were fully alert by the 3rd day, when they were extubated.

An unusual and very distinctive withdrawal syndrome appeared as the patients began to regain consciousness. The lower-extremity muscle tone remained hypotonic, but rapid violent movements occurred in the legs. These movements occurred spontaneously but could also be induced by gentle sensory stimulation to the legs. Gradually over 3 days these motions became more subdued as motor tone increased, and by 1 week the patients had returned to the same level of motor spasticity that they had had prior to intrathecal baclofen. The increase in rate and extent of spasms with reduced motor tone had been seen previously in some patients when intrathecal baclofen was suddenly withdrawn due to a catheter obstruction or a missed refill. Reinstating intrathecal baclofen in those patients immediately brought their rigidity and spasms under control again.

The two overdosed patients had no residual effects. Once the pump failure mechanism was discovered, both patients decided to restart intrathecal baclofen. No further problems with the pump have occurred, and the major clinical gains were obtained again. When medication was restarted, the patients initially required much less baclofen. The dose has had to be increased over several months in the same manner as at the beginning of the chronic trial.

Discussion

These clinical trials with continuous intrathecal baclofen infusion have demonstrated that the medication is much more effective when given in the CSF around the spinal cord than when taken orally. In fact, the clinical response has been as great or even greater than that achieved with the destructive neurosurgical procedures that have been employed in the past for spasticity. The most dramatic effect has been the reduction of abnormal motor tone. Spasms also respond well but are not completely abolished. Vigorous mechanical stimulation still results in small abortive movements. Our patients were specifically chosen because of severe rigidity and spasm which significantly interfered with daily living and caused pain, and thus the clinical response to intrathecal baclofen has met their particular needs. The largest functional gains were seen in the spinal cord-injured patients. All became more independent, and three were able to resume working. The multiple sclerosis patients had more upper-extremity impairment and consequently did not have as great a functional gain. However, they were much more comfortable and easier to care for. The improvement in bladder function and ability to sleep may have been the most significant gains in some patients.

Voluntary motor function was not restored to a significant degree in any of the patients. This is not surprising in view of the profound loss of motor function already present. In the one patient who relied on her rigidity to stand, the dose could be titrated so that function could be preserved with adequate relief of spasticity. Further testing is needed to determine whether intrathecal baclofen will help less severely spastic patients with better voluntary control.

The selection criterion was purposely narrow in this initial study, limiting the cause of spasticity to spinal cord origin. However, others have found intrathecal lumbar baclofen useful in spasticity of diffuse cerebral damage, and in children as well as adults. The purely diplegic or quadriplegic patient with cerebral palsy may well be a good candidate. More clinical trials are needed to know the range of applications of this technique.

The alternative to a destructive neurosurgical procedure for treatment of spasticity is the new pump technology and continuous delivery of medication. However, the patient is wedded to the pump and to the medical personnel serving the pump. In the future, families and patients may be able to program and refill the pump, but for the present the patients need monthly visits for filling. Higher concentrations of baclofen could be used, but then the accuracy of the pump has to be extremely precise.
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The two cases in which overdoses occurred demonstrate how prey we are to the device functioning properly. Pump failure of the type experienced in these cases had not been anticipated, and its random occurrence made diagnosis difficult. Once understood, the same pumps have been used in the continuous mode of delivery without mishap, and the manufacturer has designed and tested new pumps that do not have this problem. Fortunately, no permanent injury resulted from the overdoses, and the patients are again benefiting from the intrathecal baclofen.

A few general observations on the pharmacokinetics of baclofen can be made. A high-dose bolus of baclofen (1.5 to 4 mg) given intrathecally produces drowsiness followed by loss of consciousness and respiratory depression. This is much the same result as in animal experiments.7 Recovery takes several days. Sudden withdrawal from intrathecal baclofen results in a hyperactive state with rapid uncontrolled spasms lasting 3 to 4 days. During that period, rigidity gradually returns and seems to slow down the spasms.

The intrathecal baclofen acts on the spinal cord neurons, and 20 to 40 minutes is required to see a clinical effect from a bolus of the drug introduced into the lumbar CSF. Presumably, this time delay is due to the diffusion of baclofen from the CSF into layers II and III of the dorsal gray matter where the receptors are found.2 The half-life of the drug in the lumbar CSF is approximately 5 hours, the same as for methotrexate given by the same route.2 This undoubtedly reflects bulk flow removal. The spinal response of decreased spasticity to a bolus injection lasts up to 10 hours, even though baclofen levels in CSF have dropped to 25% of their initial level by that time. Time for diffusion of the drug from the neural tissues to CSF may account for the prolonged duration of the clinical effect.2 Slow clearance from brain tissue could also account for the long duration of coma (24 to 48 hours) seen following an overdose.1 A report that physostigmine given intravenously reverses the central effects of baclofen (G Müller-Schwefe, personal communication, 1985) may mean that an effective antagonist is available. This is currently being tested in animals. Such an antagonist would add to the safety of using intrathecal baclofen.

The gradual increase in dose needed to control spasms is a matter of concern. The change was most apparent during the first 2 to 6 months, with some leveling off afterward. However, a continued escalation in dose, with some form of gradual tolerance, could limit the effectiveness of the method. Only longer trials will provide an answer. Morphine sulfate given intrathecally has also been reported to reduce spasticity.4 We have treated two additional patients by infusion of morphine sulfate and found similar results with low continuous doses (< 2 mg/day). This raises the possibility of switching medicines if significant tolerance develops to one.

The present study indicates that intrathecal baclofen is an extremely potent drug for controlling severe spasticity for up to 2 years. The indications for its use remain to be fully explored. The success of the method underscores the potential usefulness of drug pumps to deliver medications into selected regions of the brain or spinal cord, circumventing the blood-brain barrier, providing high concentrations locally to neural tissue, and avoiding general toxicities because low doses can be employed.

References

Manuscript received May 21, 1986.
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