

INTRATHECAL BACLOFEN FOR THE TREATMENT OF DYSTONIA IN PATIENTS WITH REFLEX SYMPATHETIC DYSTROPHY

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ABSTRACT

Background Patients with reflex sympathetic dystrophy (also known as the complex regional pain syndrome) may have dystonia, which is often unresponsive to treatment. Some forms of dystonia respond to the intrathecal administration of baclofen, a specific γ -aminobutyric acid–receptor (type B) agonist that inhibits sensory input to the neurons of the spinal cord. We evaluated this treatment in seven women who had reflex sympathetic dystrophy with multifocal or generalized tonic dystonia.

Methods We performed a double-blind, randomized, controlled crossover trial of bolus intrathecal injections of 25, 50, and 75 μ g of baclofen and placebo. Changes in the severity of dystonia were assessed by the woman and by an investigator after each injection. In the second phase of the study, six of the women received a subcutaneous pump for continuous intrathecal administration of baclofen and were followed for 0.5 to 3 years.

Results In six women, bolus injections of 50 and 75 μ g of baclofen resulted in complete or partial resolution of focal dystonia of the hands but little improvement in dystonia of the legs. During continuous therapy, three women regained normal hand function, and two of these three women regained the ability to walk (one only indoors). In one woman who received continuous therapy, the pain and violent jerks disappeared and the dystonic posturing of the arm decreased. In two women the spasms or restlessness of the legs decreased, without any change in the dystonia.

Conclusions In some patients, the dystonia associated with reflex sympathetic dystrophy responds markedly to intrathecal baclofen. (N Engl J Med 2000; 343:625-30.)

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REFLEX sympathetic dystrophy, also known as the complex regional pain syndrome, is characterized by various combinations of sensory, autonomic, and motor disturbances that often follow trauma to a limb.^{1,2} Patients with this syndrome have pain and paresthesias as well as edema, changes in the temperature and color of the skin, and hyperhidrosis.^{1,2} The manifestations of motor involvement are fixed dystonic posturing, weakness, tremor, and myoclonic jerks.^{3,4} The syndrome may affect both sexes, but it is more common in wom-

en.^{1,3} Various treatments have been tried, with questionable success; they include physiotherapy, sympathetic blockade, and nonsteroidal antiinflammatory drugs.^{4,5} Splints and plaster casts have been used for the treatment of dystonic posturing, but these measures have often been ineffective.⁴

The intrathecal administration of baclofen, a specific γ -aminobutyric acid (GABA)–receptor (type B) agonist that inhibits sensory input to the neurons of the spinal cord, has proved beneficial in some patients with dystonia.⁶ In this study, we evaluated the efficacy of intrathecal baclofen in seven women with reflex sympathetic dystrophy in whom the chief clinical manifestation of the disorder was multifocal or generalized fixed dystonia.

METHODS**Patients**

Between February 1995 and June 1999, we studied seven women (mean age, 45 years; range, 33 to 63) who had had reflex sympathetic dystrophy for a mean of 13 years (range, 6 to 23). All the women met the most commonly used diagnostic criteria for reflex sympathetic dystrophy—namely, the combination of continuing pain, allodynia, or hyperalgesia, in which the pain is disproportionate to any inciting event; evidence at some time of edema, changes in blood flow to the skin, or abnormal sudomotor activity in the region of the pain; and the absence of any condition that would otherwise account for the pain and dysfunction.⁷ In addition, all seven women had progressive, sustained, tonic muscle contractions that occurred in two or more limbs and that caused fixed posturing at rest in association with various degrees of sensory and autonomic involvement (Table 1). These women were selected from 98 consecutive patients (85 of whom were women) with reflex sympathetic dystrophy who were seen at our institution over a two-year period. None of the men who were seen had multifocal or generalized dystonia, and only these seven women had such severe dystonia that invasive assessment and prolonged invasive therapy were considered justified.

In five of the women, a precipitating event (appendectomy, an ankle sprain, a neck injury, resection of the first rib, and lumbar radiculopathy in one woman each) was identified; the symptoms had begun immediately after the event in four of these women and within three months after the event in one. In all the women, the dystonia had started in the distal muscles of an arm or leg. Involvement of the arms resulted in various degrees of tonic flexion of the fingers (Fig. 1), except in one woman who had slight flexion at the metacarpal–phalangeal joints, with extension and scissoring of the fingers of both hands. Involvement of the legs resulted in inversion and flexion of the feet, with various degrees

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TABLE 1. CHARACTERISTICS OF THE SEVEN WOMEN WITH REFLEX SYMPATHETIC DYSTROPHY.

CHARACTERISTIC	NO. OF WOMEN
Pain	7
Paresthesias	7
Numbness	7
Discoloration of the skin	7
Hyperhidrosis	7
Change in skin temperature	6
Edema	6
Change in nail growth	4
Change in hair growth	2
Dystonia	7
Myoclonic jerks	7
Tremor	3

of clawing or scissoring of the toes; as a result, all seven women required the use of a wheelchair. In five of the women, the dystonia had progressed from the distal region of the limb to the proximal region or to the axial, cervical, or facial musculature. The spasms in the affected limb increased after use or after exercise in all seven women, after tactile and auditory stimulation in six of them, and at low temperatures in five. Tremor and myoclonic jerks occurred in three and seven women, respectively.

The women had been treated with analgesic drugs, levodopa, trihexyphenidyl, antiepileptic drugs, botulinum toxin (by injection), mannitol (by infusion), and surgical or chemical sympathectomy, with little benefit, and had been treated with benzodiazepines with insufficient benefit. Before starting the study, all the women underwent a trial of oral baclofen (mean dose, 50 mg per day; range, 10 to 90) for up to five months; this treatment had little or no benefit in five of the women and produced dose-limiting sedative effects in the other two. The study protocol was approved by the hospital ethics committee, and all the women gave oral informed consent.

Study Protocol

In the first phase of this study, we used a double-blind, cross-over design to evaluate the efficacy of the intrathecal administration of a bolus of baclofen. A percutaneous catheter was introduced into the lumbar subarachnoid space and the catheter tip advanced to the T11–12 level, where the catheter was left in place for five days. A computer was used to generate a random sequence of daily bolus doses of baclofen (25, 50, and 75 μg) or placebo (saline) to be given by intrathecal injection. If an adverse effect occurred after an injection, 60 percent of the volume of that injection was given the next day (without disclosure of the randomization sequence), thus reducing the risk of additional, serious adverse effects. If no adverse effects occurred, each woman received three injections of baclofen (one at each dose) and two injections of placebo.

Before and four and eight hours after each injection, each woman assessed the overall severity of her dystonia on a 100-mm visual-analogue scale on which the severity of symptoms was rated from 0 (no symptoms) to 100 (most severe symptoms). Changes in dystonia were calculated as the percentage change from the score at base line to the lower of the scores at four and eight hours. To evaluate the differences in outcome among the three injections of baclofen and the two injections of placebo, a repeated-measures analysis of variance was carried out. If a significant F ratio was obtained, a post hoc Newman–Keuls test was performed. The F ratio is a measure of the variation among groups

as compared with the variation within a group, and the Newman–Keuls test allows multiple pairwise comparisons that determine which means differ, with multiple comparisons taken into account.⁸ In addition, on each day on which an injection was given, an investigator made a qualitative assessment of the severity of dystonia and any adverse effects.

In the second phase of the study, a programmable pump (SynchroMed infusion system, Medtronic, Minneapolis) for the continuous intrathecal administration of baclofen was implanted in women in whom one or more bolus doses of baclofen resulted in an improvement in dystonia that was ≥ 50 percentage points more than the mean of the two responses to placebo. Continuous baclofen therapy was started at a daily dose two times the effective bolus dose and was adjusted for maximal effect over a three-month period. Follow-up included routine neurologic evaluations performed at visits for refilling of the pump, with specific attention to the severity of dystonia and assessments of the degree of disability.

RESULTS

Bolus Injections of Baclofen

As compared with the injections of placebo and 25 μg of baclofen, the injections of 50 and 75 μg of baclofen resulted in significant decreases in the severity of dystonia in the group of women, according to their own assessments (Table 2). In general, there was no improvement or only slight improvement in finger movements after the injections of placebo or 25 μg of baclofen, as evaluated by an investigator. After the 50- and 75- μg injections of baclofen, three women (Patients 1, 2, and 4) were able to open their hands fully, and three other women (Patients 3, 6, and 7) had substantial improvement in finger movements. After the 50- and 75- μg baclofen injections, five of the women reported a feeling of relaxation in their legs, without obvious objective improvement as assessed by the investigator. One of the women (Patient 2), who had initially required a wheelchair, was able to walk with assistance after she received the 75- μg dose of baclofen, and another woman (Patient 5), whose dystonia predominantly involved the extensor muscles, had a general feeling of relaxation, without any decrease in her dystonia. After the unblinding of the treatment medication, three women reported associating a warm feeling in the legs with the injections of baclofen.

The adverse effects related to baclofen were somnolence (in one woman), slight drowsiness (in two), muscle weakness related to hypotonia (in two), and urinary retention (in one). Somnolence interfered with the assessment of one woman (Patient 7) on one day. Five women had mild-to-moderate headache and nausea after the lumbar puncture, neither of which hampered the assessment.

Continuous Administration of Baclofen

Six women received a subcutaneous pump for continuous intrathecal administration of baclofen. The seventh woman chose not to undergo pump implantation. The mean follow-up period was 1.7 years (range, 0.5 to 3), and the mean daily maintenance dose of baclofen was 489 μg (range, 350 to 850).

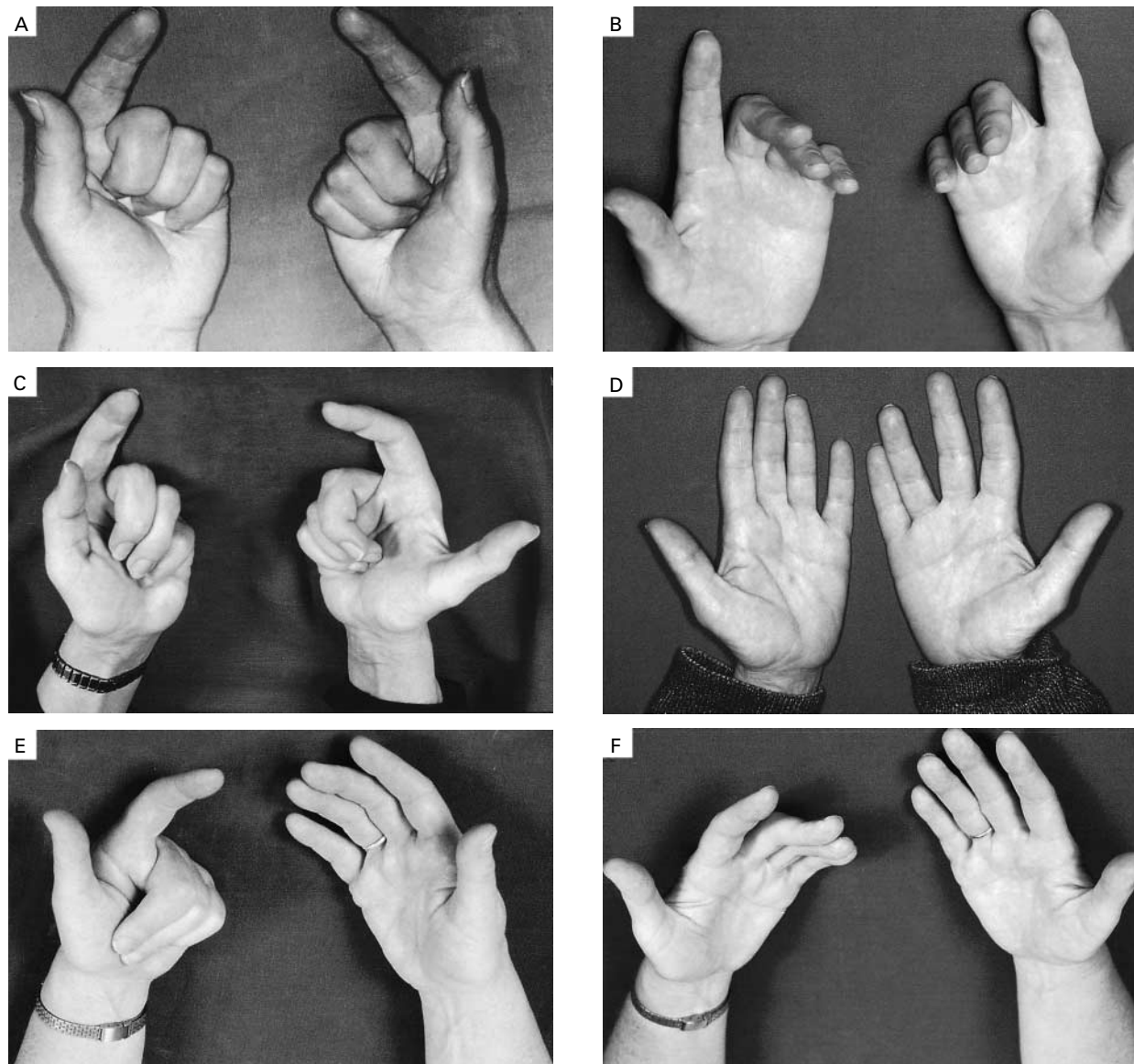


Figure 1. The Hands of Three Women before (Panels A, C, and E) and after (Panels B, D, and F) 1, 0.5, and 0.3 Year, Respectively, of Continuous Intrathecal Baclofen Therapy.

Panels A and B show the hands of Patient 1; Panels C and D, the hands of Patient 2; and Panels E and F, the hands of Patient 6.

During the first three months of continuous treatment with intrathecal baclofen, three women had complete resolution of their multifocal dystonia (Patient 6) or generalized dystonia (Patients 1 and 2). All three women regained normal hand function, although one of the women with generalized dystonia had some residual contracture. This long-term response was more marked than that seen in the first phase of the study, during which bolus injections were given. One of the women (Patient 1), who had used a wheelchair for four years, was able to walk

again within her home, and another (Patient 2) became fully ambulatory. Another woman (Patient 3) had segmental dystonia of the left shoulder, arm, and hand, and one month before pump implantation the dystonia spread to her left leg. During continuous intrathecal administration of baclofen, the dystonic posture of her shoulder resolved, the dystonia of the fingers became less severe, and the flexion postures of her elbow and wrist changed into extension postures, but the extension dystonia of the leg progressed. Despite doses as high as 1200 and

TABLE 2. PERCENT CHANGES FROM BASE LINE IN SCORES ON THE VISUAL-ANALOGUE SCALE AFTER SINGLE INTRATHECAL INJECTIONS OF PLACEBO OR BACLOFEN IN THE SEVEN WOMEN WITH REFLEX SYMPATHETIC DYSTROPHY.*

PATIENT	PLACEBO		BACLOFEN		
	FIRST INJECTION	SECOND INJECTION	25 μ g	50 μ g	75 μ g
			percent change		
1	-5	3	4	-31	-51
2	-2	1	-33	-67	-87
3	-38	-19	-51	-89	-88
4	-9	-3	1	-85	-3†
5	-4	3	-24	-36	-64
6	9	4	-6	-17	-42
7	21	-47	-17	-‡	-42†
All patients	-4 \pm 18	-8 \pm 19	-18 \pm 20	-54 \pm 30§	-54 \pm 30§

*Plus-minus values are means \pm SD. Minus signs denote a decrease in the severity of dystonia (i.e., a decrease in the score on the visual-analogue scale).

†Three fifths of the planned dose was given.

‡Because of somnolence, this woman could not be evaluated after the 50- μ g dose of baclofen.

§ $P < 0.01$ for the comparison with placebo; $P < 0.05$ for the comparison with the 25- μ g dose of baclofen.

1000 μ g per day, two women (Patients 4 and 5) had worsening of their dystonia. In both patients the possibility that the drug-delivery system had malfunctioned was ruled out.

Four women (Patients 2, 3, 4, and 5) had marked lessening or resolution of their painful muscle spasms, and two women (Patients 2 and 3) had a marked reduction in myoclonic jerks. One woman (Patient 5) reported some resolution of the restlessness of her legs.

Effects of Continuous Intrathecal Baclofen on Sensory and Autonomic Abnormalities

Three women had marked reductions in pain, four in paresthesias, two in numbness and hypothermoesthesia, and one in hypoesthesia. Other improvements included a reduction in hyperhidrosis (in one woman), decreased discoloration of the skin (in one woman), and normalization of increased nail growth (in two). One woman (Patient 6), who had an atonic bladder before implantation of the pump, regained normal bladder function after two months of baclofen therapy.

Adverse Effects during Continuous Therapy with Intrathecal Baclofen

In two women (Patients 4 and 5), atony of the bladder developed while they were receiving baclofen at doses of 120 and 270 μ g per day, respectively, and necessitated self-catheterization; in Patient 5, bladder function temporarily normalized for several months while she was receiving 730 μ g of baclofen

per day. In Patient 5, increasing the dose of baclofen to 1000 μ g per day resulted in painful, cold spots on the arms and legs and tenderness of the scalp.

DISCUSSION

We found that dystonia of the arms improved markedly in six of seven women with reflex sympathetic dystrophy after single bolus doses of baclofen given by intrathecal injection. Dystonia involving the legs improved to a lesser extent, although one woman who had used a wheelchair was able to walk with assistance after an injection. Oral baclofen had only moderate effects in some women, most likely because of its low penetration into the spinal cord and its dose-limiting sedative properties.⁹ With intrathecal administration, more of this drug is delivered to the spinal cord, and the cerebral effects of systemic treatment are eliminated.¹⁰ After pump implantation, three of the women we studied regained normal hand function, and two of them regained the ability to walk. Although we did not account for possible psychological factors in the open-label phase of the study, the beneficial responses to continuous therapy in four women were probably not the result of a placebo effect, for two reasons. First, before implantation of the pump, all the women had had progressive disease for many years. Subsequently, these women had a long-term response that developed over months and that was ultimately more marked than the response during the initial phase of the study, in which bolus doses were tested. Second, the greater improve-

ment of dystonia in the arms than in the legs in these four women also argues against a placebo effect.

Our findings are in agreement with those of other studies that found a predominance of women and girls among patients with reflex sympathetic dystrophy.^{1,3} Our findings also show that this syndrome may follow a more progressive course in women than in men.

Intrathecal baclofen therapy has been proved effective and generally safe in patients with spasticity.^{11,12} Nevertheless, complications may occur that are related to the drug or to the mode of drug delivery. Baclofen usually has few adverse effects at doses of less than 1000 μg per day, but urinary retention, constipation, and hypotonia have been reported.¹¹⁻¹³ The impaired bladder function in several of the women in our study probably resulted from the depressant effects of baclofen on the spinal centers involved in the control of micturition.¹⁴ However, disturbances in the functioning of the sphincter and detrusor muscles may also be manifestations of reflex sympathetic dystrophy.¹⁵ Problems related to intrathecal drug delivery (such as headache related to the spinal puncture; infection; and occlusion, disconnection, or breakage of the catheter) have been reported in approximately 25 percent of patients who receive medication with an intrathecal pump.^{11,16}

Our results provide evidence that neural circuits mediated by GABA are involved in reflex sympathetic dystrophy accompanied by dystonia. GABA is an important inhibitory neurotransmitter, and baclofen mimics the actions of GABA on presynaptic type B GABA receptors. Activation of these receptors results in inhibition of the sensory input to the motor neurons of the spinal cord (i.e., it results in presynaptic inhibition).^{17,18} Presynaptic inhibition can also be achieved by depolarization of primary afferent neurons, a process mediated by activation of the type A GABA receptor.¹⁹ Both mechanisms of presynaptic inhibition are mediated by the same primary afferent depolarization interneurons.²⁰ These interneurons receive an extensive amount of converging sensory and supraspinal input and therefore have a crucial role in the regulation of muscle tone and sensory perception.¹⁹ When these interneurons are impaired, motor neurons are exposed to uninhibited sensory and supraspinal input. Since flexor motor neurons and the associated interneurons that mediate depolarization of primary afferent fibers receive more sensory input than the extensor motor neurons, the preferential involvement of flexor muscles in the dystonia associated with reflex sympathetic dystrophy is not surprising.²¹

In our study, the effects of intrathecal baclofen were always more prominent in the arms than in the legs. Since T11-12 is considered the optimal position for the catheter in the treatment of spasticity of the legs in patients with spinal cord injury, this finding may indicate that afferent neurons connected to the flexor motor neurons of the arms are more sensitive to

GABAergic presynaptic inhibitory input than are the afferent neurons connected to those of the legs. However, in two of the women in our study, dystonia progressed during continuous intrathecal administration of baclofen, indicating that other mechanisms are also involved. Furthermore, dystonia characterized by extensor posturing was resistant to treatment with intrathecal baclofen. Extensor spasms have been reported after poisoning with strychnine, a glycine antagonist.²² Together, these factors may point to the involvement of glycinergic primary afferent depolarization interneurons in the development of dystonia with extensor posturing.

Some of the women in our study reported reductions in pain, sensory symptoms, and autonomic symptoms during continuous intrathecal administration of baclofen. Some interneurons that mediate primary afferent depolarization in the dorsal horn of the spinal cord exert tonic modulation of nociceptive input from primary afferent fibers to neurons of the spinothalamic tract.²³ It has been proposed that GABAergic and glycinergic mechanisms have a role in the spinal modulation of nociception and sympathetic preganglionic neuron activity.²⁴⁻²⁸

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