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Brief Report

Intrathecal Baclofen for Dystonia: Benefits and Complications During Six Years of Experience

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Summary: Fourteen patients with primary or secondary dystonia received intrathecal baclofen (ITB) through an implanted pump following a trial dose. Patients were selected for ITB trial if they had clinically unsatisfactory responses to oral antidystonic medications, including oral baclofen. Patients were rated using the Burke-Fahn-Marsden rating scale by a blinded rater after the dose of ITB was optimized. Five patients experienced improvement in symptoms as determined by a change in rating scale scores, although only two had a clear clinical benefit. Etiology of dystonia did not determine the efficacy of ITB therapy, as benefit or failure was seen in both primary and secondary dystonia. **Key Words:** Intrathecal baclofen—Dystonia.

Intrathecal administration of the gamma-aminobutyric acid (GABA) analog baclofen (beta-4-chlorophenyl GABA) (Lioresal; Medtronic, Minneapolis, MN, USA) has been demonstrated to be an effective therapy for spasticity[1–21] and for dystonia of different etiologies,[5,12,22–29] although other authors have reported less success,[30] particularly with specific types of symptomatic dystonia.[31,32] We report our experience with intrathecal baclofen (ITB) for dystonia over a 6-year period. The results and complications reported here have been previously presented in abstract form.[33,34]

METHODS

We reviewed the charts of all patients followed by the Mount Sinai Medical Center Movement Disorders Program who received ITB for dystonia (n = 14). Pumps were implanted between June 1993 and May 1998.

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Patients were considered for a trial dose of ITB if they had received extensive treatment for dystonia with oral antidystonic and antispasticity medications, including oral baclofen, without satisfactory control of symptoms or with unacceptable adverse effects. Each patient had received at minimum levodopa/carbidopa; an anticholinergic agent, usually trihexyphenidyl (Artane; Lederle, Pearl River, NY, USA); a benzodiazepine, usually clonazepam (Klonopin; Roche, Nutley, NJ, USA); and oral baclofen, often in combination, at the maximum tolerated dose. Many had also received a wide variety of other agents, including dopamine-receptor blocking agents, tetrabenazine, reserpine, carbamazepine, phenytoin, and valproic acid.

All patients received an initial trial dose of intrathecal baclofen ranging from 25 to 75 μg. If the patient had a positive response, regardless of whether it was quantitatively satisfactory, pump implantation was considered. A positive response was considered to be a reduction in symptoms as determined by both the patient and the evaluating physician. If there was no response, or equivocal benefit, and no significant side effects, the trial was repeated, usually with the dose increased by 25 to 50 μg.

The highest dose used was 200 μg. If there was no benefit and there were significant side effects, the trial was not repeated. If there was no positive response after three trials, further testing was abandoned and the patient did not proceed to surgery.

After pump implantation, the dose of ITB was increased in increments of approximately 10% until either the patient reported dose-limiting adverse effects or a dose of 1000 μg per day was achieved. If adverse effects were reported, the dose was decreased until these symptoms had resolved, and it was then increased again in smaller increments. After the highest tolerated dose had been determined, the dose was decreased in the same decrements to determine the lowest dose that produced maximal symptom reduction.

When available, videotaped examinations of patients untreated or treated with ITB were reviewed by a blinded reviewer (F.O.D.) to determine the Burke-Fahn-Marsden (BFM) Rating Scale scores.[35]

RESULTS

All patients reported here had a positive response to the trial dose except patient no. 13. The presence of mild–moderate side effects, such as sedation or nausea, in the face of clinical improvement was not regarded as a contraindication to ITB because these adverse effects can often be ameliorated with careful dose titration.

Fourteen patients with dystonia had pumps implanted (Table 1). Eight had primary generalized dystonia, one primary cranial segmental dystonia, and five had secondary dystonia. Of 14 patients with dystonia (primary and secondary), five showed objective benefit, two unequivocally (patient nos. 4 and 14), and three less so (patient nos. 5, 8, and 10). The response to oral baclofen did not predict the response to ITB, although this information was obtained retrospectively and was not objectively assessed. Two patients reported an improvement with oral but not intrathecal baclofen. Only one of the five patients who had objective benefits from ITB had a slight benefit from oral baclofen.

Mean length of therapy for dystonia was 29 months (range, 6–64 mos). Mean dose of those continuing was 590 μg per day (range, 50–1000 μg per day). Frequently, increasing symptoms prompted dose increases. Patient no. 11 with symptomatic dystonia had not had the dose optimized at the time of this report.

Primary Dystonia

Fourteen patients with the DYT1 mutation were screened with ITB; nine of these proceeded to pump implantation. Of nine patients with generalized dystonia, eight had a positive response and proceeded to surgery. Of five with idiopathic cranial segmental ± brachial dystonia, only two responded positively to the trial and one went on to have a pump placed.

Seven of the nine patients with primary dystonia had videotape evidence adequate to perform BFM ratings on and off ITB. Of these, a decrease in BFM scores was seen in three patients (patient nos. 4, 5, and 8; Fig. 1). Only one patient (patient no. 4) reported a subjective benefit with improved ability in ambulation. Despite the reduction in scores of patient nos. 5 and 8, both subsequently had the dose tapered and the pump removed without exacerbation of symptoms. Patient no. 2, who

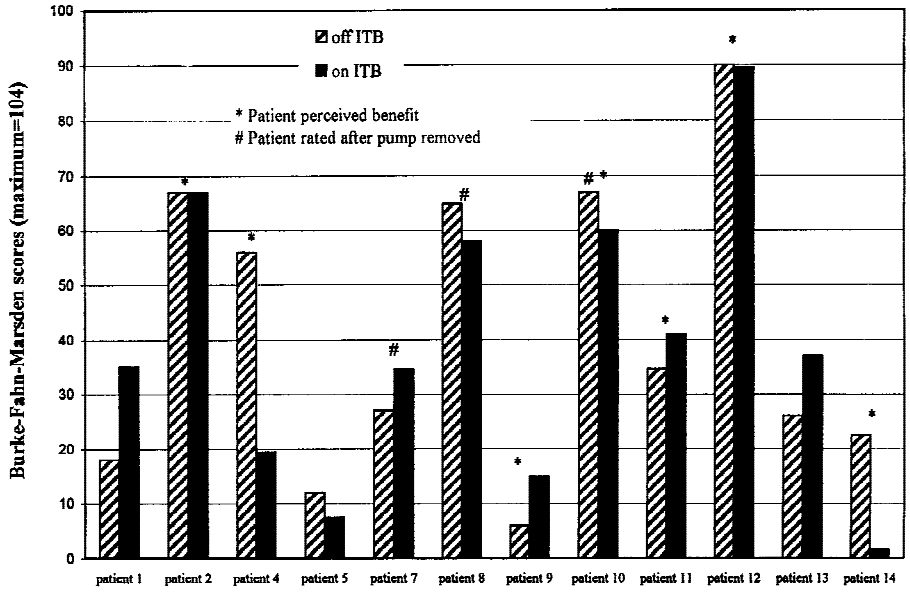

FIG. 1. Burke-Fahn-Marsden scores on and off ITB rated on videotape by a blinded rater. Speech is not included. In some cases (*) patients perceived benefit which was not reflected in rating scale scores. Videotape data was not available for patient nos. 3 and 6.

TABLE 1. *Patients with dystonia treated with intrathecal baclofen*

Patient no.	Age at onset/ sex	Age at pump implan-tation (yrs)	Length of follow up with ITB (mos)	Diagnosis, previous surgery	Distribution	Pre-implantation maximum dose of oral baclofen (mg); effect	Complications	Effect	Blinded video–rated BFM scores (maximum = 104)		Outcome/ current dose (μg/day)
									Off ITB	On ITB	
1	10/F	24	36	ITD/DYT1	Generalized	160; benefit	Low volume alarm failure (asympt.)	None	18	35	630
2	7/M	34	6	ITD/DYT1	Generalized	30; no benefit	—	Subjective benefit, able to lie flat	67	67	Death-suicide 690
3	7/F	33	64	ITD/DYT1, bilateral thalamotomy	Generalized	120; reduced pain, no effect on dystonia	Wound breakdown at 4 wks	Subjective benefit	75.5	N/A	Pump replaced 676
4	8/F	60	32	ITD/DYT1, left thalamotomy	Generalized	40; impaired balance	—	Able to ambulate	56	19.5	400
5	7/F	51	10	ITD/DYT1, bilateral thalamotomy	Generalized L > R	N/A; no benefit	—	None	12	7.5	Pump removed; no benefit
6	8/F	19	41	ITD/DYT1	Mild generalized	80; no benefit	Catheter fracture (asymptomatic)	None	1.5#	N/A	Pump removed; no benefit, complication
7	10/M	30	20	ITD/DYT1	Generalized, especially cranial	150; no benefit	Wound dehiscence ×2, underper-fusion (symptomatic)	None	27#	34.5	Pump removed; no benefit, repeated complications
8	12/F	42	36	ITD/DYT1, bilateral thalamotomy	Generalized	90; no benefit, sedation	—	None	65#	58	Pump removed; no benefit
9	55/F	63	49	ITD	Cranial segmental	40; no benefit, lethargy	Moderate overdose	Subjective benefit	6	15	440
10	19/F	48	60	Perinatal hypoxia	Generalized, R > L	20; no benefit, depression	Catheter fracture, underperfusion (both asympt.)	Benefit to left arm and leg	67#	60	235
11	2/F	22	6	CNS disease of unknown etiology/ seizures; negative work-up	Generalized, L > R	40; no benefit, slurred speech, sedation	—	Subjective benefit to arm, leg, speech	34.5	41	50
12	5/M	44	7	Primary putaminal degeneration of unknown etiology	Generalized	N/A; no benefit	—	Subjective benefit to speech, swallowing	90	89.5	Death-cardiac 900
13	47/M	63	15	?Tardive dystonia; normal MRI, negative work-up	Generalized, extensor	40; slight benefit	—	None	26	37	1000
14	42/M	44	22	Tardive dystonia	Upper extremities	140; slight benefit	—	Benefit; reduced akathisia	22.5	1.5	880

CNS, central nervous system; MRI, magnetic resonance image; asympt., asymptomatic; DYT1–DYT1 mutation haplotype: ITD, idiopathic torsion dystonia; N/A, not available; BFM, Burke-Fahn-Marsden; # rating performed after pump removed.

had no change in BFM score, reported a subjective benefit in that he was able to lie flat in bed. Patient no. 9, who had a worsening of BFM score, also reported a subjective benefit in terms of a reduction in cranial dystonic movements. No patient had a change in the distribution of dystonia.

Four patients (patient nos. 1, 3, 4, and 9) continue with ITB. One patient (patient no. 2) committed suicide. Four patients had pumps removed, either following complications (patient nos. 6 and 7) or following demonstration of lack of efficacy (patient nos. 5 and 8). Three patients (patient nos. 1, 7, and 9) demonstrated a worsening of BFM scores on treatment.

Patient no. 1 was the only patient reporting benefit from oral baclofen; however, she did not respond to ITB.

Secondary Dystonia

Seven patients with symptomatic dystonia were screened; five of these proceeded to pump implantation.

All patients who had a positive trial, that is, three with generalized symptomatic dystonia and one with upper extremity tardive dystonia, proceeded to pump placement. In the case of patient no. 13, the response to the trial dose was equivocal even on repeat evaluation, but the patient elected to undergo implantation with the rationale that he might nevertheless benefit from continual infusion of medication. One patient with generalized dystonia with caudate/putamen disease of unknown etiology and one patient with post-traumatic leg dystonia had negative responses and did not receive a pump.

Five patients had secondary dystonia, one case each resulting from delayed-onset dystonia from perinatal hypoxia, tardive dystonia, presumed tardive dystonia, putaminal degeneration of unknown etiology,[36] and one of unknown etiology associated with complex partial seizures. All five had blinded BFM evaluations with two demonstrating objective clinical benefit from ITB (Fig. 1).

Patient no. 10 who had perinatal hypoxia had significant improvement in relaxation of her right lower extremity, and this was demonstrated as a small decrease (10%) in BFM scores. However, she did not report a worsening of symptoms either when her pump underperfused or when the catheter fractured, suggesting a possible placebo effect. Patient no. 14 who had tardive dystonia had a dramatic improvement of both his dystonia and akathisia as reflected by his BFM scores (22.5 to 1.5); this patient had a slight benefit from oral baclofen, whereas patient no. 10 had significant side effects which limited dose escalation of the oral medication.

Patient no. 11, who had symptomatic dystonia of unknown etiology associated with seizures, had an increase in BFM scores (16%), but reported an improvement in speech fluidity, limb dexterity, and gait. Patient no. 12, who had putaminal degeneration, had no change in BFM scores but demonstrated improvement of swallowing with weight gain and reported improvement of comprehension of his speech by strangers. Patient no. 13 had slight benefit from oral baclofen but his BFM scores increased on ITB.

Four patients continue ITB therapy. One patient (patient no. 12) died of cardiac causes unrelated to ITB.

DISCUSSION

ITB is an accepted effective therapy for patients with spasticity of both spinal and cerebral origins.[1–20,37] Significant benefit has been demonstrated as a reduction in tone and spasticity, and is also reflected in studies of quality of life, activities of daily living, level of function, and cost-effectiveness.[12,16,18,38]

ITB may be considered as an option for selected patients with intractable dystonia.[32,39,40] Ford[30] reported on 13 patients with dystonia who underwent pump implantation; our patient no. 7 was also included in their report. Similar to our experience, they failed to demonstrate a consistent or predictable significant difference in dystonia and disability scores following ITB. Their patients were only evaluated using the Burke-Fahn-Marsden scale at the time of the ITB trial, when the dose is not optimized. Six of their 13 patients (46%) self-reported sustained benefit, as did eight of 14 (62%) of our patients, for example, reporting improvements in comfort or in activities of daily living. Surprisingly, two of our patients whose BFM scores worsened (patient nos. 9 and 11) and two patients whose scores were unchanged (patient nos. 2 and 12) reported symptomatic benefit. This may have been the result of a placebo effect or insensitivity of the rating scales. Additionally, two patients (patient nos. 6 and 10) had catheter fractures without an acute worsening of symptoms. Thus, it may be helpful for all patients receiving ITB for dystonia to undergo blinded dose reduction to clarify whether they are indeed deriving benefit from this therapy.

The response to oral baclofen was not objectively or prospectively assessed in this study, but on chart review it did not appear to predict the response to ITB. The response rate to oral baclofen (3 of 14 = 21%) did not differ from that reported in the literature.[41,42]

The etiology of the dystonia and DYT1 status did not predict the response to ITB, because patients with both primary and secondary dystonias of varying etiologies benefited or failed. The most striking improvement was in the patient with tardive dystonia. Dressler has also reported benefit in a patient with tardive dystonia.[25]

One of our dystonia patients receiving ITB committed suicide. He had severe, generalized idiopathic dystonia and had just had a personal psychologic trauma (sudden, unexpected death of his main source of psychologic support) and was not noted to be depressed before this event. Another of our patients who received ITB for spasticity also committed suicide. He had progressive disability secondary to multiple sclerosis, which is known to increase the risk of suicide.[43–50] There has been no evidence in our other patients of depression related to ITB, and this is not reported in the literature, although suicidal ideation and suicide attempt are noted in the manufacturer's labeling. Despite the apparent precipitants of suicide in these two patients, a relationship with ITB cannot be excluded, and patients receiving ITB should be monitored for signs and symptoms of depression.

Most of the equipment-related complications we report are similar to those reported elsewhere.[8,9,51–53] Im-

provements in technology, and education and experience of both the patient and the healthcare provider may reduce the occurrence of these events in the future.

ITB may exacerbate hyperkinetic movements as reported by Silbert[31] in a case of secondary dystonia resulting from a metabolic disorder. Ryan[55] reported a case of a patient receiving oral baclofen for spasticity secondary to spinal stenosis who developed dyskinetic movements. We observed increases in BFM scores in five patients on ITB. This effect was not so pronounced clinically as to suggest exacerbation by ITB, but was only revealed on analysis of BFM scores; thus, we suspect that this change reflected disease progression. However, we cannot apply this interpretation to the case (patient no. 7) in which the off-ITB score was obtained after removing the pump, suggesting that ITB did indeed exacerbate his symptoms.

In summary, our clinical experience with ITB for dystonia suggests that this therapy may be helpful for select patients, but we are unfortunately not yet able to determine in advance who will benefit and who will not. Equipment-related complications are fairly common, may be serious and limit therapy, and may necessitate further invasive procedures. Of 14 patients with dystonia (primary and secondary), five showed objective benefit, two unequivocally, and three less so. Development of tolerance may be a significant problem, and in some patients we have been unable to achieve the apparent benefit attained with the trial dose. Other complicating factors requiring further study are the difficulty in distinguishing the development of tolerance from progression of disease and day-to-day fluctuations in symptoms. Blinded dose reduction is suggested to determine sustained efficacy.

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