Intrathecal Baclofen for Intractable Spinal Spasticity – a Double-blind Cross-over Comparison with Placebo in 6 Patients

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ABSTRACT: A group of six subjects with intractable spinal spasticity completed a double-blind cross-over paradigm in which they received two intrathecal bolus injections of baclofen solution five hours apart on two different days and two intrathecal bolus injections of placebo saline five hours apart on two other days. Each subject was repeatedly tested with a battery of clinical and physiological tests. In contrast to the placebo injections, the group responded to the baclofen injections with subjective and objective, clinically significant improvement in parameters of spasticity in their lower limbs, including muscle tone, frequency of spasms, hyperreflexia and passive range of joint motion. Furthermore, this improvement was maintained following thirty consecutive days of intrathecal bolus injections of baclofen at a fixed dose.

RÉSUMÉ: Baclofen intrathécal dans la spasticité spinale réfractaire — comparaison avec un placebo en double aveugle et chassé-croisé chez six patients. Un groupe de six sujets avec spasticité spinale réfractaire ont complété un paradigme en double aveugle et chassé-croisé dans lequel ils ont reçu deux injections d'un bolus intrathécal de baclofen en solution à cinq heures d'intervalle pendant deux jours et deux injections d'un bolus intrathécal de salin comme placebo à cinq heures d'intervalle deux autres jours. Chaque sujet a subi à plusieurs reprises une batterie d'épreuves cliniques et physiologiques. Contrairement aux injections de placebo, le groupe a répondu aux injections de baclofen par une amélioration subjective et objective, cliniquement significative, des paramètres de spasticité aux membres inférieurs, incluant le tonus musculaire, la fréquence des spasmes, l'hyperréflexie et l'amplitude des mouvements articulaires passifs. De plus, cette amélioration a été maintenue sur une période de trente jours consécutifs d'injections d'un bolus intrathécal de baclofen à dose fixe.

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Baclofen [B-1-(p-chlorophenyl)-aminobutyric acid] (Lioresal- Ciba-Geigy), a putative GABA-b receptor agonist, depresses monosynaptic and polysynaptic neuronal transmission and probably relaxes muscles by reducing overall spinal reflex excitability.[1] Young and Delwaide[2] consider balcofen to be the most effective agent for the treatment of spasticity. Its oral use is limited by side effects such as somnolence, confusion, weakness and ataxia, attributed to the large doses required because of its poor penetration into the central nervous system.[3] Kroin et al.[4] reported that baclofen could be safely administered into the spinal subarachnoid space, and that this resulted in a dramatic inhibition of polysynaptic reflexes. Subsequently Penn and Kroin[5] reported a reduction in muscle tone for 5 to 8 hours without the dose-limiting side effects of oral baclofen, and suggested that intrathecal baclofen might provide effective control of intractable spasticity. These effects of intrathecal baclofen appear to be dose-related and attributed to its direct action on the neuronal pool in the superficial layers of the spinal cord in a manner similar to that described for intrathecal opiates.[6] Many subjects have already been implanted with drug-delivery systems for chronic intrathecal baclofen administration.[7-17] In fact, chronic intrathecal baclofen administration is currently recommended by Siegfried and Lazorthes[18] as the treatment of choice for intractable spasticity.

Armstrong et al.[7] and Penn et al.[19] reported that the spasmolytic effects observed from intrathecal baclofen therapy were not placebo effects; but, only a few studies such as these were designed specifically to measure the magnitude of the placebo effect of intrathecal therapy as well as the magnitude of the baclofen effect. Treatments for spasticity are difficult to evaluate because of difficulties in measuring spasticity. Neurophysiological measurements seldom have clinical relevance and clinical observations have generally been considered too subjective.[20] Clinical and physiological changes may be isolated, inconsistent or contradictory so that reliance on only one or two parameters may lead to incorrect conclusions. For example, we were unable to confirm the benefits of electrical spinal cord stimulation reported by others in spastic cerebral palsy with a multidisci-

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plinary protocol.[21-23] Therefore before we commenced studies of chronic intrathecal baclofen infusion, we first conducted a protocol which incorporated a double-blind cross-over paradigm of intrathecal baclofen and placebo saline with repeated measures of multiple clinical and physiological parameters.

Methods

The components of the study are summarized in Table 1. The study following six phases.

Phase 1 – recruitment and baseline tests

Entry criteria for study subjects are described in Table 2. Subjects were admitted to hospital and weaned off all spasmolytics over a 10 day period. If a myelogram or MRI of the spine had not been performed within 12 months of entry into the study, one or both was repeated in order to confirm a patent subarachnoid space and to exclude any associated pathology amenable to specific treatment such as a posttraumatic syrinx. Twelve tests were then administered in order to describe and quantify their spasticity and its impact.

Phase 2 – preliminary trial injections of intrathecal baclofen

A percutaneous nylon catheter (Concord/Portex, Keene, New Hampshire, U.S.A.) was introduced into the lumbar subarachnoid space at L3, 4 under sterile conditions. A test dose of only 10 μg baclofen solution (Ciba-Geigy Canada Ltd.) was then injected into the subarachnoid space and subjects were observed hourly for changes in vital signs, muscle tone and strength. Additional doses in increasing increments of 5-10 μg were injected at 24 hour intervals until an objective reduction in muscle tone was observed in the legs.

Phase 3 – implantation of subcutaneous catheter access port (CAP) and determination of an individual dose

The percutaneous catheter was removed and a lumbar subarachnoid catheter and access port (CAP - Shiley Infusaid Infuse-A-Port™) was implanted under sterile conditions in the operating room. Subjects were then given daily percutaneous bolus injections into their CAP in 5 μg increments and encouraged to resume full mobility while monitoring their muscle tone and strength in response to each dose and its duration of action in order to determine an optimum individual dose for each subject. We focused on the ability of the intrathecal baclofen injections to diminish the intractable trunk and lower limb spasms evident in each subject. Accordingly, in the subjects afflicted only with trunk and leg spasm, we increased the dose of baclofen in increments until the subjects reported the first appearance of weakness in their upper extremities and then dropped back to a dose that avoided such weakness. In subjects with preserved motor control in their lower limbs, we adjusted the dose so as to preserve their ability to transfer. In the quadriplegic subject with concurrent intractable upper limb spasms, the dose was escalated until tone in the upper limbs was also reduced.

Once an individual therapeutic dose of baclofen was determined for each subject, the drug was allowed to wash out for 48 hours.

Phase 4 – cross-over paradigm of intrathecal baclofen and intrathecal saline

This phase comprised an 11 day cycle. Subjects were randomized to receive their individual therapeutic dose of intrathecal baclofen either on days 2 and 8 and an identical volume of saline on days 5 and 11; or, saline on days 2 and 8 and baclofen on days 5 and 11 (see Table 1). Thus, treatments were separated by a 48 hour washout interval. The time of the bolus injections was kept constant. In the 5 subjects whose individual daily dose consisted of a single bolus dose, a treatment consisted of a single intrathecal injection of the treatment solution at 0800 hours. In the one subject whose individual daily dose consisted of two bolus injections, a treatment consisted of 2 injections of the treatment solution at 0800 hours and at 1300 hours.

The concentration of the baclofen solution was adjusted by the hospital pharmacy so as to deliver the individual dose in volumes of between 1.0 and 2.5 ml. Subjects and examiners were blind to the nature of each treatment.

All twelve tests conducted in phase 1 were repeated on day 1 to ascertain variation in the baseline scores, on each treatment day and on days 4 and 7, 24 hours following the washout of the first baclofen treatment and the first saline treatment (see Table 1).

Table 1: Overview of the Conduct of the Study

STUDY PHASE	1	2	3	4											5	6
Day Number				1	2	3	4	5	6	7	8	9	10	11		1....30
Wean from all spasmolytics	x															
Percutaneous SA Catheter		x														
Baclofen 10 μg Trial Dose		x														
Implant Permanent SA Catheter + CAP			x													
Baclofen Increments to Optimum Dose			x													
Baclofen at Optimum Dose[1]					x						x					x.....x
Placebo Saline[1]								x						x		
Tests	x			x	x		x	x		x	x			x		x
Preliminary Analysis															x	
Final Analysis																x

[1] - The order of baclofen and saline during phase 4 is assigned by randomization
SA = Subarachnoid
CAP = Catheter access port

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Table 2: Eligibility Criteria

1.	Age 16 - 60 years
2.	Spastic secondary to spinal cord lesions caused by trauma or multiple sclerosis.
3.	Reversible spastic predominantly in the lower limbs and trunk.
4.	Independent in the community and ambulatory at least by wheelchair.
5.	Failure of optimum pharmacotherapy and physiotherapy.
6.	Exclusion of underlying disorders such as systemic illness, known to precipitate and exacerbate spasticity.
7.	Confirmation of normal spinal CSF flow by myelography or MRI.
8.	No prior ablative therapy to the spinal cord, roots, peripheral nerves or muscles.
9.	No prior tenotomies and fusions at hips, knees or ankles.
10.	No known allergy to baclofen.

The sequence and time of testing during the day was always kept constant.

Phase 5 – preliminary analysis

A preliminary analysis was conducted on the tests that generated numerical scores, comparing the averaged scores for each treatment against the baseline scores in order to determine whether a treatment effect was evident and whether it differed for the baclofen treatments and the saline treatments.

Phase 6 – daily bolus injections of intrathecal baclofen for 30 consecutive days

Subjects who demonstrated a significant reduction in spasticity from baclofen as opposed to saline at an Alpha of 0.05 during phase 4, were instructed in the sterile technique of bolus administration of baclofen into their CAP either by self-administration or by a family member or caregiver. The subjects were then discharged on a schedule of daily bolus injections of their individual therapeutic dose of intrathecal baclofen and encouraged to resume their normal daily activities in the community. The dose of baclofen was kept constant for 30 days, following which subjects were retested in order to determine whether the baclofen effect had been maintained (see Table 1).

In order to reduce the risk of overdose and to monitor compliance with sterile technique and the dose schedule, the baclofen solution was prepared in individual single dose ampoules by the hospital pharmacy, so as to deliver the individual therapeutic dose in a volume of less than 2.5 ml. These single dose ampoules were dispensed weekly when the injection sites over the CAPs were examined.

Tests

Twelve tests were administered, including a questionnaire; clinical tests of motor tone, strength and activities of daily living; urodynamic tests; and, the flexor reflex test.

1. The questionnaire was a modification of the one employed in our previous study of spasticity in which subjects were asked to rate the effects of their spasticity on daily activities such as toiletry, grooming, etc. with a numerical visual analog scale from 0 to 5 in which 5 represents maximum disability.[21]

2. A modification of the Ashworth Scale of resistance to passive movement which had previously been shown to have good interrater reliability.[24,25] This test incorporates a 6-point score for each muscle group tested, (e.g. hip flexors, hip adductors, quadriceps, hamstrings, etc.) with 0 indicative of flaccidity and 5 indicative of extreme hypertonicity.

3. A spasm score which rates the presence of spontaneous spasms and the ease of provoking spasms during active and passive movements of the upper and lower extremities and trunk with a 5-point scale in which 0 is complete flaccidity and 4 represents continuous spontaneous spasms.[13]

4. A reflex score that grades the presence and intensity of the biceps, triceps, patellar and achilles tendon reflexes with a 5-point scale in which 0 represents hypotonic areflexia and 4 extreme hyperreflexia.

5. The amount of impairment of passive joint motion in degrees for hip flexion-extension, hip abduction-adduction, knee flexion-extension, ankle dorsi-plantar flexion and comparable motion at the shoulders, elbows and wrists. A change of greater than 5 degrees was considered significant. Normal values were taken from the manual of the American Academy of Orthopedic Surgeons.[26] Armstrong et al.[7] found that this test demonstrated some of the most striking differences among their children receiving intrathecal baclofen.

6. Strength was recorded using the classical 6-point clinical grading[27] in which a score of 5 indicates normal strength and a score of 0 indicates a lack of voluntary contraction. In the lower limbs, we measured hip flexion and abduction, knee flexion and extension, ankle dorsiflexion. In the upper limbs we measured shoulder abduction, elbow flexion and extension, wrist dorsiflexion and grip.

7. A timed evaluation of dressing that we have used before[21] in which subjects were given 5 minutes to perform a given dressing task such as removing a pair of socks or slacks. The time to complete each task is measured and a performance score is also assigned.

8. The Smith Hand Function Evaluation[28] which is a common timed test used to measure manual dexterity.

Urodynamic studies included:

9. A cystometrogram

10. A recording of the urethral pressure profile

11. Measurements of voiding flow rates.

Our neurophysiological study consisted of:

12. The flexor reflex study of the quadriceps, biceps femoris, gastrocnemius and anterior tibial muscles.[29] Subjects were always tested in the supine position with legs extended. Silver chloride surface electrodes were taped on the skin over muscle bellies and the signal was amplified through a conventional EMG amplifier. Precise location of electrodes was recorded for each patient relative to anatomical landmarks for consistency from session to session. A special hand-held mechanical stimulator was used that incorporated a force-calibrating device, providing feedback to the examiner by 3 light-emitting diodes corresponding to high-medium-low force so as to enable the examiner to maintain a consistent 2-second, medium range force for all cutaneous plantar stimulations. The resultant EMG signal was rectified and averaged for 7 stimulations at each session with a Digital PDP 1134 computer.

Analysis of Data

At the preliminary analysis in phase 5, the scores of each subject's clinical tests which generated numerical data were averaged by treatment and compared against each other and the baseline scores using the Wilcoxon Signed-Ranks Test for pairs of treatment. For the clinical tests, upper limb scores and lower limb scores were compared as subtests of each of the tests.

Statistically significant treatment effects

For the final analysis, we calculated not only the magnitude of the placebo and baclofen effects over the baseline, but also the effect of baclofen treatment against such placebo manipulation. The results of the tests and subtests conducted during the two baclofen and the two saline treatments in phase 4 were averaged by treatment. The results after 30 consecutive days of intrathecal baclofen injections were considered separately. The Wilcoxon Signed-Ranks Test for pairs of treatments was used to conduct both individual and group analyses because the subjects formed a heterogeneous group with varying degrees of disability from their underlying illness and spasticity; and, the test results for the various subtests were not expected to conform to normal distributions.

Clinically significant treatment effects

We defined the following criteria for clinically significant treatment effects at the beginning of the study: a) mean treatment scores had to lie outside the 95% confidence limits about the other treatment mean and the baseline mean; or, b) mean treatment scores had to differ from the other treatment mean and the baseline mean by a value of at least 1.0 for tests rated by a 4 to 6 point scale, where the 95% confidence limits were less than 1.0.

Descriptive analyses

The urodynamic tests generated numerical data but were only suitable for descriptive analysis. Accordingly, results were rated independently by a urologist as improved, unchanged or worsened from baseline values for each individual subject by treatment and then case into tables.

For the flexor reflex test, the area of the averaged signal envelope of muscle activity induced by stimulation was measured as uV.sec and adjusted for a standard duration of the stimulus. Means of the area of the signal envelopes were calculated for each subject and compared for each treatment. This standard duration of the stimulus was the average duration of all stimulations for a particular subject during individual analyses; but, for the group analysis, a standard duration of 2.0 seconds stimulus duration was used for consistency among subjects. The threshold for significant change was arbitrarily set at a 50% change from the area of the signal envelope during placebo treatment and the number of subjects who demonstrated such change were tabled by treatment.

Disability index

The scores of the questionnaire, passive range of motion of the lower limbs, spasm score for trunk and legs, motor tone and strength of the lower limbs were used to create a disability index for each subject by treatment. The normal strength scores were reversed so as to reflect degree of weakness rather than strength by assigning a score of 0 instead of 5 for normal strength and 5 instead of 0 for complete paralysis. The scores of each of the 5 tests were then summed by treatment (baseline, placebo, baclofen and 30-day baclofen treatments) and compared against the baseline to derive a fraction of the baseline. The fractions for the 5 tests were added and averaged in order to give equal weighting to the five tests and to derive a disability index as a fraction of 1.0 for each treatment.

Results

Six subjects who satisfied the eligibility criteria described in Table 2 consented to participate in this study – four with post-traumatic spasticity following spinal cord trauma and two with multiple sclerosis (see Table 3). All were afflicted with intractable trunk and leg spasms. One also suffered from intractable spasms in his upper limbs. All six were confined to a wheelchair. Only one had sufficient residual voluntary movement in his lower limbs to enable him to transfer to a standing posture with a walker. All had previously used oral baclofen to their individual maximum tolerable dose. Three had discontinued oral baclofen altogether because of undesirable side effects.

Two subjects had discontinued oral spasmolytics prior to admission. No episodes of psychosis were observed when the remaining four subjects were weaned from their spasmolytic medications. Two subjects reports very transient hallucinations.

Table 3: Subjects

No.	Age	Sex	Etiology	Deficit	Distribution of Spasms	Maximum Tolerated Dose of Baclofen	Spasmolytic Medication at Recruitment
1	41	F	Trauma	Complete motor paraplegia T8 × 4 yrs	Trunk & Legs	Baclofen 90 mg/day	Tizanidine 80 mg/day
2	41	F	M.S.	Paraparesis × 5 yrs	Trunk & Legs	Baclofen 120 mg/day	Baclofen 120 mg/day Valium 5 mg/day
3	29	M	Trauma	Complete motor quadriplegia × 3 yrs	Arms, Trunk & Legs	Baclofen 20 mg/day	Baclofen 20 mg/day Valium 30 mg/day
4	35	M	M.S.	Paraplegia T8 × 6 yrs	Trunk & Legs	Baclofen 120 mg/day	Nil
5	28	M	Trauma	Incomplete motor quadriparesis C4 × 6 yrs	Arms, Trunk & Legs	Baclofen 120 mg/day	Baclofen 120 mg/day Valium 30 mg/day
6	29	M	Trauma	Complete motor	Trunk & Legs	Baclofen 80 mg/day	Nil

M.S. = Multiple sclerosis

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Table 4: Baclofen Dose

Subject	Initial Threshold Response Dose	Individual Optimum Bolus Dose
1	20 micrograms	25 micrograms – single bolus
2	30 micrograms	125 micrograms – single bolus
3	30 micrograms	100 micrograms – single bolus
4	10 micrograms	50 micrograms – single bolus
5	10 micrograms	15 micrograms @ 0800 hrs 7.5 micrograms @ 1300 hrs
6	20 micrograms	75 micrograms – single bolus

Test dose of baclofen

Motor tone in the lower limbs was consistently reduced in all six subjects following single bolus injections of intrathecal baclofen. Two subjects responded to the initial 10 μg test dose of baclofen, two others to 20 μg and the remaining two to 30 μg (see Table 4).

Magnitude of the optimum therapeutic dose

The dose of baclofen could be titrated to specific end points such as the reduction of muscle tone to flaccidity. The individual therapeutic dose differed for each subject and bore no relationship to the intensity, distribution or etiology of their spasticity. In a quadriplegic subject with intractable upper and lower limb spasms (subject 3), the dose was titrated so as to reduce his intractable upper limb spasms as well as his trunk and lower limb spasms without suppressing respiration. Attempts at reducing minor upper limb spasms in another quadriparetic subject (subject 5) created disabling leg weakness. Therefore his dose was titrated to reduce his trunk and leg spasms only, while maintaining sufficient tone and voluntary motor activity so that he could stand.

Onset and duration of action of baclofen

The spasmolytic effect of baclofen appeared 30 to 60 minutes following each dose with an initial duration of 16 to 20 hours which contracted within days to 8 to 10 hours. No changes occurred in vital signs. By the end of the month of daily bolus injections, the duration of action had stabilized at approximately 6 hours for each subject.

Treatment effects during phase 4

As a group, subjects demonstrated a baclofen treatment effect on the questionnaire scores, lower limb tone, trunk and leg spasms, lower limb reflexes and in the passive range of motion for upper and lower limb joints ($p < .05$). The effect was also clinically significant in all these tests except for the passive range of motion in the upper limb joints.

The treatment effects on individual subjects are summarized in Table 5. Significant baclofen treatment effects were observed in the reduction of lower limb tone and spasms in all 6 subjects, in improved questionnaire scores in 5, and in improved passive range of motion in the lower limbs in 4 ($p < .05$). Our quadriplegic subject with intractable spasms of his trunk and all four limbs (subject 3) also demonstrated a significant baclofen treatment effect on reducing the tone in his upper limbs. Another subject (subject 2) developed additional weakness in her leg muscles while on baclofen, although this did not affect her transfers. The baclofen treatment effects were clinically significant for a reduction in lower limb tone in all 6 subjects, for reduced trunk and lower limb spasms in 5, for reduced lower limb reflexes in 4, for questionnaire scores in 3, for improved passive range of motion in the legs in 2, for diminished tone and reflexes in the arm in one subject and for the additional lower limb weakness in another subject.

Placebo treatment effects were only observed in subjects who also demonstrated baclofen treatment effects. In each instance, the magnitude of the placebo treatment effect was much smaller than the baclofen treatment effect. Placebo treatment effects were evident for lower limb tone in 4 subjects, for improved passive range of motion in the legs in 3, for reduced trunk and leg spasms in 2, and for an improved questionnaire score in 2 and for reduced upper limb tone in 1 subject ($p < .05$). These effects were clinically significant in only 1 subject (subject 6) for reduced tone, spasms and reflexes in the lower limbs.

Treatment effects during phase 6

Three subjects injected themselves during phase 6 while the remaining three subjects received their daily injections from family and caregivers. As a group, subjects maintained the baclofen treatment effect observed during phase 4 with the exception of a loss of effect on lower limb reflexes and passive range of motion of upper limb joints. However, with the exception of a slight additional improvement in passive range of motion in the legs, the magnitude of the treatment effect for the group diminished somewhat. Nevertheless, the effect remained clinically significant for all tests except the questionnaire scores.

Table 5: Number of Subjects with Treatment Effects by Test

Test Parameter	Placebo	Treatment Baclofen-1	Baclofen-2
Less Disability *per questionnaire*	2	5 (3)	3 (3)
Greater ROM – Arms	0	0	0
Greater ROM – Legs	3	4 (2)	3 (1)
Reduced Spasm Score in arms	0	0	0
Reduced Spasm Score in legs	2 (1)	6 (5)	5 (5)
Reduced Tone in arms	1	1 (1)	1 (1)
Reduced Tone in legs	4 (1)	6 (6)	6 (6)
Reduced Strength in arms	0	0	0
Reduced Strength in legs	0	1 (1)	2 (2)
Reduced Reflexes in arms	0	(1)	0
Reduced Reflexes in legs	(1)	(4)	(3)

Treatment effects at an alpha of 0.05 using the Wilcoxon Signed-Ranks Test for pairs of treatments. Placebo treatment was compared against baseline and the two baclofen treatments were compared to placebo treatment. All significant baclofen treatment effects over placebo were also significant over baseline. Numbers in brackets indicate the number of subjects who demonstrated clinically significant treatment effects.

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It is evident from Table 5, that only one subject (subject 1) lost her baclofen treatment effect after 30 consecutive days of bolus injections at a fixed dose.

Disability index

The disability index, as a fraction of the baseline disability score, is depicted by subject and by treatment in Figure 1. All subjects demonstrated a considerable reduction in their disability index during the baclofen treatments in phase 4. Five maintained this effect during phase 6. A placebo reduction in disability was also evident for 5 of the 6 subjects but of reduced magnitude compared to that of the baclofen treatment effect.

Flexor reflex test

Only one subject demonstrated a placebo response characterized by a 50% reduction in the size of the muscle electrical activity envelope. Four subjects demonstrated such a response during single day baclofen treatment and 3 subjects still showed such a response after 30 days of intrathecal baclofen injections at a fixed dose.

Other test results

Despite the spasmolytic effects observed on the trunk and legs of all subjects, scores for the timed dressing test did not change appreciably nor did the scores for the Smith Hand Function Evaluation. On the other hand, the urodynamic parameters improved in response to baclofen treatment in 2 subjects. In both of these subjects there was an increase in bladder volume without a concomitant change in intravesicular pressure. In one subject (subject 5) volumes increased from an average of 234 ml at baseline to 327 ml while receiving baclofen during phase 4. During the same interval, the bladder volume of our spastic quadriplegic subject (subject 3) increased from an average of 238 ml to 397 ml, enabling him to convert from an indwelling foley catheter to intermittent catheterization during phase 6.

Side effects and complications

One subject (subject 2) experienced mild somnolence following each of the first four doses of baclofen during phase 3. No other undesirable side effects were reported or observed throughout the study.

There were no instances of equipment failure or sepsis once the CAP and lumbar catheter were satisfactorily introduced. Two subjects required initial repositioning of their lumbar catheter at the time of insertion during phase 3.

Discussion

Because chronic intrathecal baclofen infusion through a chronic infusion device is costly, a preliminary study was conducted to determine whether the effects of intrathecal baclofen differed from placebo treatment and whether the treatment effect could be maintained for a month.

The evaluation of new treatments against disabling spasticity is difficult. Spasticity varies in intensity among and within subjects.[20,30,31] This makes it difficult not only to measure changes in spasticity from treatment, but also to discriminate such changes from placebo effects. Five of our six subjects demonstrated a placebo treatment effect in some test results and at least one subject, the magnitude of this effect was clinically significant. Accordingly, paradigms that measure the effects of treatments for spasticity must include placebo manipulations and several clinical and physiological tests.

Our analysis confirmed that the spasmolytic treatment effects of baclofen exceeded the placebo effects. Despite the fact that our clinical tests had been used by others,[13,19,32] there was a risk that some of our observed differences might eventually prove

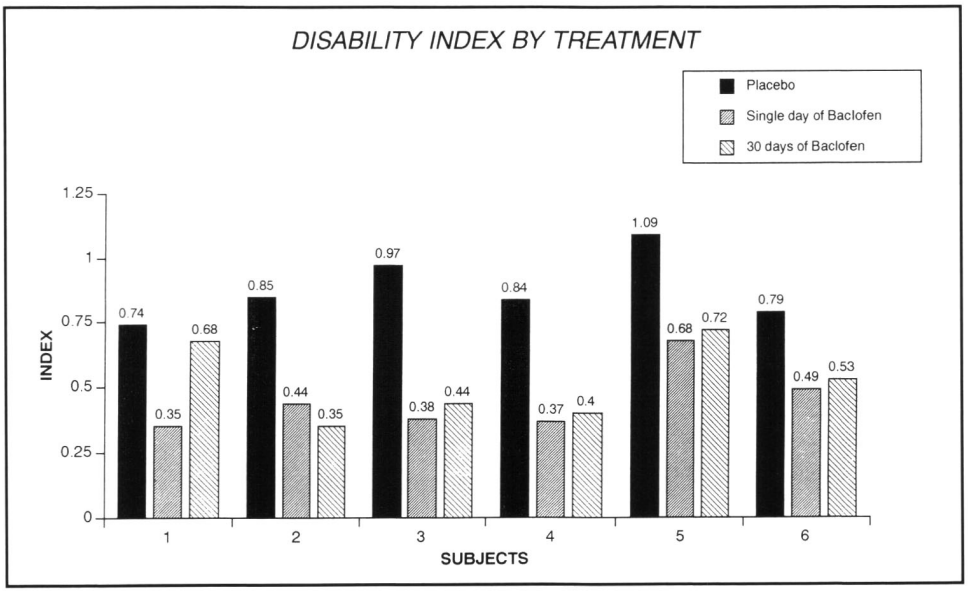

Figure 1 — Disability Index calculated by equally weighting the total test scores for Disability Questionnaire, Passive Range of Motion of Lower Limb Joints, Spasm Score for Trunk and Legs, Motor Tone for Legs, and Degree of Weakness in Legs. The Baseline Index was set at 1.0. The Disability Index for the treatments are a fraction of the Baseline Index.

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meaningless since the tests had not been properly validated. Therefore, we defined criteria for clinical significance by consensus at the beginning of the study. Then, by applying those criteria to the data, we found only a few discrepancies between statistically and clinically significant baclofen treatment effects in contrast to the placebo treatment effects which were predominantly statistical effects without clinical significance. Hence, we believe that the data confirm that the spasmolytic effects of baclofen that we observed were clinically relevant.

In small studies such as this, one must interpret differences among treatments with caution, even when such differences appear highly significant with conventional methods. Therefore, we conducted both individual and group analyses and confirmed that the group as a whole also demonstrated the treatment effects found in individual subjects.

In each instance, the benefit of intrathecal baclofen on lower limb tone and trunk and leg spasms was immediately evident with the first few bolus injections of baclofen. When this individual treatment effect on tone and reflexes was clinically significant, it was maintained after a month of injections, suggesting that a lengthy trial of chronic bolus injections is not required. However, concurrent motor weakness induced by the reduced tone may negate some potential functional gains,[33] suggesting that for at least some subjects, a functional assessment and measurements of overall well-being are also important outcome measures.

In order for such outcome measures to fully reflect the effect of intrathecal baclofen, the treatment must be continued long enough to enable a subject to resume his or her normal daily routine. Hence, in contrast to the limited number of bolus injections of baclofen administered by Penn et al.[19] prior to implanting a chronic infusion device, we currently recommend a trial of intrathecal baclofen bolus injections of sufficient duration to facilitate a functional appraisal. We recognize that the need for a long period of intrathecal bolus injections must be weighed against the risks of inadvertent overdose and infection.[34,35] By carefully instructing subjects, relatives and caregivers in the technique of repeated bolus injections into a subcutaneous reservoir and by monitoring the injection sites frequently, we encountered no such complications during this study. Leavens et al.[36] also avoided such complications from chronic intrathecal bolus injections of narcotics.

The group analysis revealed that the statistically significant and the clinically significant treatment effects of baclofen were maintained after 30 consecutive days of intrathecal bolus injections (see Table 5). However, the magnitude of this treatment effect was diluted after 30 days. This may reflect the fact that the baclofen dose was kept constant and was not titrated to maintain a specific level of treatment effect during this 30 day interval. The need for escalating doses during the first 3 months of chronic baclofen infusion is well recognized.[13,17]

Note that all of our subjects demonstrated an initial response to a 10 to 30 μg bolus dose of intrathecal baclofen. Therefore, in order to avert an initial overdose, we caution others against using initial bolus doses of 25 or more μg recommended by others.[7,14,17,37,38] Instead, we recommend starting with an initial bolus dose of 10 μg followed by small incremental increases of only 5 to 10 μg.

Upon completion of this study, subjects were provided with individual dose ampoules of baclofen solution in order for them to continue daily bolus injections until they had an opportunity to consider conversion to a chronic infusion device. The baclofen was dispensed weekly in order to facilitate monitoring. In contrast to the fixed dose that was administered during phase 6 of the study, doses were now adjusted as required for each individual subject in order to optimize spasmolysis. The results of such chronic daily bolus administration of intrathecal baclofen will be reported separately.

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