

The Use of Baclofen in Treatment of Spasticity in Multiple Sclerosis

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SUMMARY: *Baclofen was used in a double-blind crossover placebo-controlled trial to treat spasticity in patients with multiple sclerosis (MS). While on Baclofen, patients obtained a significant ($p < 0.001$) reduction in spasticity compared to controls. The drug was particularly effective in alleviating flexor and extensors spasms, as well as their associated pain. Side effects were common in this study, but were usually well tolerated by the patients. The commonest side effects*

were sedation, nausea and vomiting. There were no changes in hepatic, renal, or hematological function in any patients. Increased weakness due to loss of spasticity for support was also a fairly common complaint. The drug seems best indicated in patients in whom spasticity is not required for support or other activities of daily living. Careful monitoring of the patient is essential for effective use of this drug.

RÉSUMÉ: *L'emploi du Baclofen et le traitement de la spasticité dans la Sclérose en plaques.*

Le Baclofen fut employé dans le traitement de la spasticité de patients atteints de sclérose en plaques lors d'un essai à double insu avec technique croisée et contrôle placebo. Lors de ces essais, les patients au Baclofen eurent une diminution significative ($p < 0.001$) de la spasticité, par rapport aux sujets témoins. Le médicament s'est révélé particulièrement efficace contre les spasmes en flexion ou en extension, ainsi que contre la douleur qui les accompagne. Il y eut au cours de cette étude de nombreux

effets secondaires, mais il étaient généralement tolérés par les patients. Les effets secondaires les plus fréquents furent la sédation, la nausée et le vomissement. Il n'y eut aucune modification des fonctions hépatiques, rénales ou hématologiques. Une plainte commune fut l'augmentation de la faiblesse des membres inférieurs due à la perte de la spasticité qui permettait le soutien. Le médicament est donc préférable chez les patients pour qui la spasticité n'est pas nécessaire à la station debout ou pour les autres activités quotidiennes. Il est essentiel de suivre de près chacun des patients pour assurer les meilleurs résultats.

INTRODUCTION

The medical treatment of spasticity, a disabling problem of patients with multiple sclerosis (MS), is, at present, inadequate. Poor understanding of the pathogenesis of spasticity is acknowledged (Laundau, 1974; Lancet Editorial, 1970).

Diazepam and dantrolene sodium are the major drugs presently in use. Their troublesome and sometimes serious side effects, as well as ineffectiveness in many cases, limit their usefulness (Calne, 1975; Sachais, 1977). The ideal drug in the treatment of spasticity is still being sought. Baclofen, a GABA analogue, has been suggested as one possible drug.

The use of baclofen in the treatment of spasticity has evolved in the following manner. GABA was the first neurotransmitter thought to have inhibitory properties. GABA does not readily cross the blood brain barrier (Roberts, 1975), but baclofen (available in Canada as Lioresal, Ciba-Geigy) does. Assuming an action similar to GABA, baclofen began to be used in the treatment of spasticity in several countries, beginning in 1966.

The mechanism of action of baclofen is still not understood. Reduction of presynaptic inhibition was suggested as a major factor contributing to the hyperexcitability of motor neurons, with spasticity the result (Burke and Ashby, 1972). Since one of GABA's major actions was to increase presynaptic inhibition (Curtis, 1971), it was assumed that baclofen would act in a similar manner. This assumption has not been borne out by recent research (Burke et al, 1971; Ashby and White, 1973; Davidoff, 1974; Curtis, 1974). Baclofen may be a selective inhibitor of an excitatory neurotransmitter,

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substance "P" (Saito, 1975) or its effect may be mediated by its phenylethylamine moiety, rather than its GABA-analogue portion (Curtis, 1974).

The metabolism of baclofen has recently been reviewed (Faigle, 1971; Sachais, 1977). The drug is effective orally, and has been shown to have no serious side effects in terms of hepatic, renal, or hematological function. Nausea and vomiting, as well as sedation, are the commonest side effects reported in the literature. Baclofen has been shown to be useful in treating spasticity from a variety of causes: MS, spinal disorders such as trauma, and spasticity secondary to stroke (Pinto, 1971; Hudgson, 1971; From, 1975; Pederson, 1970).

The drug has been reported to be most beneficial in spasticity secondary to MS (Feldman, 1978; Sachais, 1977; Palacek, 1971). Clinical experience with the drug in Canada has been limited (Ashby, 1973; Lapierre, 1974).

The authors set out to gain more experience with this drug in treating spasticity in patients with MS. Baclofen was effective in treating spasticity in our patients, and it was particularly effective in relieving extensor and flexor spasms. A major problem, as with other antispastic agents, has been that reduction in spasticity may result in weakness. Deterioration of activities such as sitting and walking may ensue. This has been noted by previous authors (Pedersen, 1970). The side effects have been frequent, but are usually well tolerated. Close monitoring of the patient is mandatory for most effective use.

METHOD

A double-blind cross over placebo-controlled format was employed to study lower limb spasticity in 21 patients with clinically definite MS or chronic myelopathy (presumed MS). The patients were otherwise well. Informed consent was obtained in each case. Drugs such as diazepam or steroids which could effect muscle tone were stopped at least seven days prior to entering the trial. Each subject was randomly allocated to the use of baclofen or placebo for twenty-one days. After a wash-out period of seven

days, a second phase, using the alternate treatment, was instituted. Baclofen (10 mg. tablets) was given orally and was identical to placebo in size, shape, color and taste. Each drug was administered in gradually increasing doses (beginning with 5 mg. three times a day with meals) until the patient reached 60 mg. or until intolerable side effects resulted. The patients were seen weekly and blood pressure, pulse, and weight were assessed each time. Biochemical analysis of hepatic, renal, and hematological function was performed before, during the wash-out period, and at the end of the trial.

A reliable test of spasticity is not yet available. The authors chose a test which was considered objective, reproducible, and easily done at the bedside. Spasticity in the legs was graded at the end of each phase, independently by two observers, in the following manner. After the patient had rested in bed, supine for five minutes, spasticity was graded 1 to 5 by an assessment of tone in the extensor muscles of the knee. The leg was passively flexed at the hip and the degree of tone in the quadriceps muscles was assessed by the time taken for the leg to fall to the bed. The time required for the heel to touch the bed was recorded and graded appropriately (see Table 1). When there was a difference in the score between the legs, the higher score was recorded. Other parameters such as extensor and flexor spasms, gait function, and bladder function were also evaluated by history and physical examination

and recorded on a separate protocol provided by Ciba-Geigy Company (see Saichais, 1977, for details). These latter results were analysed separately from the assessment of quadriceps tone.

RESULTS

Twenty one subjects entered the trial, fifteen male and six female, with a mean age of forty-nine and thirty-six years, respectively. The mean duration of illness in the males and females was fourteen and nine years, respectively.

The mean grade of spasticity before treatment with baclofen was three and after treatment was two, with a mean score change of one. The mean grade of spasticity before the use of placebo was three and was unchanged by the use of placebo.

While on placebo, no subject exhibited a detectable change in spasticity. While on the active agent, thirteen out of eighteen patients showed an objective improvement in spasticity (sign test $p < .001$). Only one patient used a contaminating drug during this study (diazepam, 5 to 7 mg., used for night-time sedation). There were 3 withdrawals from the study (see below) The analysis of the results from a protocol, provided by Ciba-Geigy Company, showed a similar benefit in reducing both flexor and extensor spasticity in the legs. In addition, baclofen decreased clonus, flexor and extensor spasms, and their associated pain.

The most common side effects in this series were sedation, nausea, and

TABLE I:
Grading of Spasticity

0	Normal — no spasticity
1	Increased deep tendon reflexes with a tendency for the leg to jerk several times before falling to the bed after passive flexion of the knee and hip
2	Same phenomenon as in No. 1 plus a slow drift (less than 15 seconds) of the leg to the bed
3	The drift is slower, between 15-30 seconds
4	After passive flexion at the knee and hip, the leg will remain extended for a period of 30 seconds or more
5	In the absence of voluntary contraction, the leg will stay extended and require a significant degree of force to overcome the extensor spasticity

vomiting (see Figure 1). The incidence of side effects, overall, was high, with 71% of the patients on the active agent having at least one side effect, compared to only 19% of those on placebo. This incidence is somewhat higher than that recently reported, although Sachais (1977) reported somnolence occurred in 75% of his patients. Fortunately, the side effects were usually well tolerated by the subjects. However, side effects did restrict the total dosage in two patients and accounted for withdrawal from the study in one. Increased weakness, such that walking became impaired, sometimes causing the patients to fall, occurred in three patients. This resulted in withdrawal from the study in one patient and restricted the maximum dosage in two. Two patients had an episode of neurological worsening, with signs and symptoms specific enough to allow a diagnosis of an exacerbation of MS — one in the placebo group and one in the active group. The exacerbations were mild, lasting from three to six weeks, with good recovery in each case. Two other patients had complaints other than increased weakness or balance disturbance, which seemed to be a worsening of their underlying condition. In these two cases, the symptoms were not specific enough to make a diagnosis of an acute relapse of MS. One of these patients was on placebo and other on baclofen. The symptoms were mild and did not restrict dosage or result in withdrawal from the study in either case.

There were no changes in blood pressure, pulse, hepatic, renal, or hematological function in any of the patients. One patient gained about 4 kg. and described a bloating sensation of the abdomen and legs. Her blood pressure remained normal, and there was no evidence of edema. The symptoms regressed after stopping the baclofen. (This patient was later re-challenged with the drug on an open trial and again had similar symptoms without any weight gain).

Eleven patients were given the drug on an open trial basis for six months, with close follow-up. The dosage of baclofen ranged from 30 to 200 mg. per day. Seven patients continued to have sustained relief of spasticity. The

drug had to be withdrawn from two patients who were taking up to 200 mg. per day. One of these patients developed a severe discomfort in the legs which necessitated discontinuing the drug. The second patient, although clearly benefitting from the drug, developed an acute depression which may or may not have been related to the use of baclofen.

DISCUSSION

Baclofen proved to be an effective drug in the treatment of spasticity in patients with MS. It resulted in sustained relief for at least six months. The authors were especially impressed with the ability of this drug to alleviate extensor and flexor spasms and the associated discomfort these spasms may cause. Sometimes the relief of these spasms was the only manifestation of the efficacy of the drug, as objective testing of tone failed to reveal any change. Patients were often delighted with the relief of spasms.

Secondly, it was found that the treatment of spasticity with baclofen was not uniformly beneficial in all patients. The authors could not find

any clinical parameters which would predict which patients would respond and which would not. It was noted, however, that those patients who had no side effects were also those who had no response.

The frequency of side effects was found to be high in this series. In general, they were transient and occurred when the drug was being increased or the dosage was very high (eg. 200 mg. per day). The patients usually accommodated to the side effects quickly. There was a variable sensitivity from patient to patient in development of and the accommodation to the side effects.

It was disturbing to the authors that some patients deteriorated while using this drug. Several patients obviously required spasticity for support in walking. When this spasticity was withdrawn, their gait deteriorated dramatically. The authors concluded that the drug was not indicated in such patients. The drug seemed best indicated in non-ambulatory patients who do not require spasticity for any activities of daily living and in whom

Figure 1
Side Effects of Baclofen

	NUMBER (%)	MEAN DURATION (DAYS)	SEVERITY
NEUROLOGICAL			
SEDATION	6(29)	15	1,1,2,3,3,3
HEADACHE	3(14)	6	3,3,3
MOOD CHANGES			
EUPHORIA	4(19)		
DEPRESSION	2(10)	9	1,2
DEPRESSION	2(10)	9	3,3
DIZZINESS (NONSPECIFIC)	2(10)	16	1,1
BALANCE DISTURBANCE	2(10)	6	2,4
INCREASED WEAKNESS	3(14)	18	2,4,4
GASTROINTESTINAL			
NAUSEA	5(24)	8	1,2,2,3,4
VOMITING	2(10)	5	2,2
DIARRHEA	1(5)	14	5
ABDOMINAL PAIN	2(10)	5	2,4
MISCELLANEOUS			
GENERAL MALAISE	2(10)	14	2,2
DRY MOUTH	1(5)	16	2
WEIGHT GAIN	1(5)	21	3
1 — MILD			
2 — MODERATE			
3 — SEVERE			
4 — PROHIBITIVE			

their spasticity was a hindrance to nursing and self-care.

It was even more disturbing to the authors that the use of the drug was associated with a definite relapse of the MS in one case. Although mild and short-lived, the possibility that this drug may have been responsible for the relapse is worthy of attention. Further study is required to ascertain whether the observed associated relapses of MS in this series were merely chance occurrences or actually precipitated by the drug.

The authors found it necessary to closely supervise their patients, when beginning the drug, because of the frequency of side effects and the problems of deterioration of function in some patients. Careful selection is necessary in order to avoid the use of baclofen in those patients whose spasticity is of obvious benefit in ambulation. Patients should be seen frequently and the dosage adjusted according to the reaction of the individual.

The authors recommend that the drug be given starting with small doses (5 mg. three or four times a day) taken with meals. The drug should be slowly increased every two or three days, or even longer, until a dosage of 60 to 80 mg. a day is reached. If weakness should occur, or severe side effects ensue, the drug should not be further increased or should be reduced or stopped. Only after the patient has accommodated to the side effects and/or increased weakness should the dosage of the drug be increased.

The authors conclude that baclofen is effective in treating spasticity in some patients with MS. Further studies with this drug are indicated.

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