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.

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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Baclofen was effective in treating
spasticity from a variety of
causes: MS, spinal disorders such as
trauma, and spasticity secondary to
stroke (Pinto, 1971; Hudson, 1971;
From, 1975; Pederson, 1970).
The drug has been to report 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 (Asby, 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
steriods 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. 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 appropri­
ately (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, respectivly.
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,
seventeen 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>
<thead>
<tr>
<th>Grading of Spasticity</th>
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<tbody>
<tr>
<td>0 Normal — no spasticity</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>2 Same phenomenon as in No. 1 plus a slow drift (less than 15 seconds) of the leg to the bed</td>
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<tr>
<td>3 The drift is slower, between 15-30 seconds</td>
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<tr>
<td>4 After passive flexion at the knee and hip, the leg will remain extended for a period of 30 seconds or more</td>
</tr>
<tr>
<td>5 In the absence of voluntary contraction, the leg will stay extended and require a significant degree of force to overcome the extensor spasticity</td>
</tr>
</tbody>
</table>
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 a 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 benefiting 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 accomodation 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

<table>
<thead>
<tr>
<th>NUMBER (%)</th>
<th>MEAN DURATION (DAYS)</th>
<th>SEVERITY</th>
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</thead>
<tbody>
<tr>
<td>NEUROLOGICAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEDATION</td>
<td>6(29)</td>
<td>15</td>
</tr>
<tr>
<td>HEADACHE</td>
<td>3(14)</td>
<td>6</td>
</tr>
<tr>
<td>MOOD CHANGES</td>
<td>4(9)</td>
<td>2,4</td>
</tr>
<tr>
<td>EUPHORIA</td>
<td>2(10)</td>
<td>9</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>2(10)</td>
<td>9</td>
</tr>
<tr>
<td>DIZZINESS (NONSPECIFIC)</td>
<td>2(10)</td>
<td>16</td>
</tr>
<tr>
<td>BALANCE DISTURBANCE</td>
<td>2(10)</td>
<td>6</td>
</tr>
<tr>
<td>INCREASED WEAKNESS</td>
<td>3(14)</td>
<td>18</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAUSEA</td>
<td>5(24)</td>
<td>8</td>
</tr>
<tr>
<td>VOMITING</td>
<td>2(10)</td>
<td>5</td>
</tr>
<tr>
<td>DIARRHEA</td>
<td>1(5)</td>
<td>14</td>
</tr>
<tr>
<td>ABDOMINAL PAIN</td>
<td>2(10)</td>
<td>5</td>
</tr>
<tr>
<td>MISCELLANEOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENERAL MALAISE</td>
<td>2(10)</td>
<td>14</td>
</tr>
<tr>
<td>DRY MOUTH</td>
<td>1(5)</td>
<td>16</td>
</tr>
<tr>
<td>WEIGHT GAIN</td>
<td>1(5)</td>
<td>21</td>
</tr>
</tbody>
</table>

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.

REFERENCES