Baclofen in Parkinson’s disease

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Summary In a controlled trial, baclofen (mean dose 45 mg daily) significantly increased disability from Parkinsonism in 12 patients with the long-term levodopa syndrome. Peak dose choreoathetosis was not improved but benefit was observed in all four patients with “off period dystonia.” Adverse side effects were common and severe, and included visual hallucinations, vomiting, and dizziness.

Baclofen (β-parachlorophenyl gammabutyric acid) is an analogue of gamma-aminobutyric acid (GABA) used in the treatment of spastic disorders. It has been shown in animal studies to affect central dopamine metabolism in a complex dose-dependent way (Fuxe et al., 1975), and to depress the firing rate of dopaminergic nigral neurones (Olpe et al., 1977). It is uncertain, however, whether this effect is exerted through GABA synapses (Davies and Watkins, 1974; Anden and Wachtel, 1977), or occurs as a direct effect on dopamine receptors. On the assumption that baclofen is a GABA agonist, it has been used to treat the chorea of Huntington's disease (Barbeau, 1973), tardive dyskinesias (Korsgaard, 1976), and schizophrenia (Frederiksen, 1975; Bigelow et al., 1977), and has been shown to aggravate neuroleptic-induced Parkinsonism (Gerlach, 1977). As a result of a previous report in which a patient with idiopathic Parkinson’s disease on levodopa developed visual hallucinations, abnormal involuntary movements, and reduced levodopa tolerance after the abrupt withdrawal of baclofen (Lees et al., 1977a), the effect of baclofen on levodopa-treated Parkinsonism has been investigated.

Patients and methods

Twelve patients with idiopathic Parkinson’s disease (seven male, five female, mean age 66 years, mean duration of disease 12 years, and mean disease severity grade 3 on the Hoehn and Yahr classification) agreed to take part in a double-blind within-patient crossover trial. All the patients were taking levodopa in combination with a peripheral decarboxylase inhibitor (mean dose 600 mg), and had received levodopa for a mean period of six years. Marked oscillation in performance and abnormal involuntary movements were present in all patients. Patients were assessed at intervals of 14 days by the same observer and their disability recorded using the Columbia University Disability Scale and a four-point scale for abnormal involuntary movements. An initial daily dose of 10 mg baclofen was increased at weekly intervals by 10 mg up to an arbitrary maximum of 90 mg daily in divided doses while levodopa therapy remained constant. After a minimum period of two weeks on maximum tolerated doses of baclofen and at varying intervals, a placebo was substituted unknown to the assessor or the patient and continued for two weeks.

Results

The Table shows that baclofen significantly aggravated rigidity and functional capacity. Only two patients attained a dose of 90 mg daily, and two patients were unable to tolerate baclofen at all and withdrew from the trial. Choreoathetosis and oscillations in performance on peak dosage of levodopa were unchanged by baclofen; however

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Active</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor (one component)</td>
<td>15 (1.5 ± 0.83)</td>
<td>10 (1.0 ± 0.63)</td>
<td>NS</td>
</tr>
<tr>
<td>Bradykinesia (five components)</td>
<td>160 (16.0 ± 3.44)</td>
<td>142 (14.2 ± 3.25)</td>
<td>NS</td>
</tr>
<tr>
<td>R rigidity (one component)</td>
<td>19 (1.9 ± 0.83)</td>
<td>13 (1.3 ± 0.64)</td>
<td>P &lt; 0.1</td>
</tr>
<tr>
<td>Functional capacity (six components)</td>
<td>111 (11.1 ± 1.45)</td>
<td>92 (9.2 ± 1.47)</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>
in four patients with morning dystonia, there was
reduction in pain and severity of dystonia.

ADVERSE SIDE EFFECTS
Side effects were more frequent than in the treat-
ment of spastic disorders. Visual hallucinations
occurred in two patients and in a further patient
during placebo phase. Toxic confusional states
(three patients), nausea (three patients) vomiting
(two patients), headaches (two patients), giddiness
(two patients), unsteadiness (one patient), and
malaise (one patient) were also reported.

Discussion
Baclofen aggravated levodopa-treated idiopathic
Parkinson’s disease in this study. It is possible,
however, that the deterioration occurred as a
consequence of increased adverse reactions since
there is no available evidence to suggest that
baclofen alters central dopamine metabolism in
man (Walinder et al., 1977). Disturbances of the
mesolimbic and mesocortical dopaminergic sys-
tems have been claimed to be responsible for some
of the long-term psychiatric disturbances of lev-
dopa treatment such as visual hallucinations
(Damasio and Castro Caldas, 1975). The frequency
of this complication with baclofen is of interest
as animal studies have shown it to have more
powerful effects on mesolimbic systems (Fuxe
et al., 1975).

Flexion dystonia and, more rarely, segmental
dystonia occur in untreated Parkinson’s disease
(Denny-Brown, 1962) and are usually aggravated
by levodopa (Duvoisin et al., 1972). We have re-
cently described torsion and segmental dystonia
occurring for the first time after a mean period of
three years of levodopa treatment in patients with
pronounced oscillations in performance. This side
effect occurred most commonly on rising in the
morning and was relieved by the first dose of
levodopa, which then usually resulted in choreo-
athetosis on peak dosage (Lees et al., 1977b). Baclofen
was found in this study to benefit morning
dystonia in all four patients, relieving pain and
improving posture. Similar results were also ob-
erved with diazepam, 5 mg three times daily.

Baclofen might, therefore, have a place in the
treatment of levodopa-induced off-period dystonia
in Parkinson’s disease. Its use, however, must be
supervised closely as toxic adverse reactions are
common.

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