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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 arbitary 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.

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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 *Effects of baclofen on patients studied*

	Scores ± SD		
Clinical features	*Active*	*Placebo*	*Significance*
Tremor (one component)	15 (1.5 ± 0.83)	10 (1.0 ± 0.63)	NS
Bradykinesia (five components)	160 (16.0 ± 3.44)	142 (14.2 ± 3.25)	NS
Rigidity (one component)	19 (1.9 ± 0.83)	13 (1.3 ± 0.64)	$P < 0.1$
Functional capacity (six components)	111 (11.1 ± 1.45)	92 (9.2 ± 1.47)	$P < 0.01$

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 treatment 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 systems have been claimed to be responsible for some of the long-term psychiatric disturbances of levodopa 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 recently 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 choreoathetosis 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 observed 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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