Budipine Provides Additional Benefit in Patients With Parkinson Disease Receiving a Stable Optimum Dopaminergic Drug Regimen

Horst Przuntek, MD; Stefan Bittkau, MD; Harald Bliesath, MD; Ulrich Böttner, MD; Gerd Fuchs, MD; Joachim Glass, MD; Harald Haller, MD; Thomas Klockgether, MD; Peter Kraus, MD; Lutz Lachenmayer, MD; Dieter Müller, MD; Thomas Müller, MD; Bernhard Rathay, MD; Jörg Sgonina, PhD; Volker Steinijans, PhD; Elemer Teshmar, MD; Gudrun Ulm, MD; Dieter Volc, MD

Background: The complex pharmacological profile of the antiparkinsonian drug budipine influences neurotransmission beyond the dopaminergic system. Previous studies have demonstrated the therapeutic efficacy of budipine on motor symptoms in insufficiently treated patients with Parkinson disease.

Objective: To demonstrate the efficacy of 20 mg of budipine, 3 times daily, in addition to a stable, prior, optimum-titrated dopaminergic substitution consisting of a combination of levodopa and a dopa decarboxylase inhibitor, bromocriptine mesylate, and optional selegiline hydrochloride in 99 patients with idiopathic Parkinson disease in a multicenter, double-blind, placebo-controlled trial.

Results: Budipine significantly (\(P<.001\)) decreased the Columbia University Rating Scale sum score (median, 15.0; 95% confidence interval, 11.3-17.0) compared with placebo (median, 4.3; 95% confidence interval, 3.0-7.5) at study end point. Budipine reduced Columbia University Rating Scale subscores for tremor, rigidity, and akinesia.

Conclusion: The additional application of budipine provides further therapeutic benefit in subjects with Parkinson disease receiving a stable, prior, optimum-titrated dopaminergic drug regimen because of the hypothetical positive impact of budipine on altered nondopaminergic neurotransmission in patients with Parkinson disease.

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Antiparkinsonian drug trials have mainly focused on the substitution of the nigrostriatal dopaminergic deficit and have mainly resulted in improvement of parkinsonian motor symptoms. But insidious deteriorating neurodegeneration also affects other neurotransmitter systems and extranigral anatomical structures in patients with idiopathic Parkinson disease (PD). Thus, the neurodegenerative process causes onset of a wide heterogeneous variety of parkinsonian features, all of which limit quality of life. Therefore, compounds with a complex pharmacological profile, which also influences neurotransmission beyond the dopaminergic system, may hypothetically provide an additional therapeutic benefit in patients with PD. Budipine represents such a drug, because it also influences, for instance, GABAergic, norepinephrinergic, serotonergic, and cholinergic neurotransmission. Eltze provides a review. Previous clinical trials have demonstrated the therapeutic efficacy of budipine on motor symptoms in subjects with PD who receive an insufficient antiparkinsonian drug regimen. Przuntek and Müller provide a review. The objective of this multicenter, placebo-controlled, double-blind clinical trial was to demonstrate the antiparkinsonian efficacy of budipine in addition to a stable, prior, optimally titrated dopaminergic drug regimen consisting of a combination of levodopa and a dopa decarboxylase inhibitor, bromocriptine mesylate, and optional selegiline hydrochloride.

RESULTS

There was a significant distinct reduction of the CURS sum score in the budipine-treated patients compared with the placebo-treated patients (Table 2 and Figure 2). The improvement of the median CURS score corresponded to nearly 40% in the budipine-treated group. Columbia University Rating Scale subscores for tremor, rigidity, and akinesia were significantly more reduced in the budipine- than the placebo-treated subjects (Table 2). Scores for depression and dementia did not significantly change within and between both groups (\(P=.12\) and \(.29\), respectively; Wilcoxon rank sum test). Dizziness (\(n=4\)), dry mouth (\(n=4\)), loss of appetite (\(n=3\)), nervousness (\(n=3\)), and visual dysfunction (\(n=3\)) were reported adverse effects of the budipine-treated patients, whereas only 1 participant in the pla-
PATIENTS AND METHODS

PATIENTS

We enrolled 99 patients with idiopathic PD, according to the United Kingdom Brain Bank criteria, into the study (Figure 1).14 They were randomized to treatment with budipine (n=49; Hoehn and Yahr stage II [n=2], III [n=17], IV [n=18], or V [n=3] [totals reflect patients who completed the trial]) or placebo (n=50; Hoehn and Yahr stage II [n=4], III [n=16], IV [n=20], or V [n=4] [totals reflect patients who completed the trial]) by chance. Their drug regimen had to consist of a combination of levodopa/a dopa decarboxylase inhibitor, bromocriptine, and optional selegiline. Their Columbia University Rating Scale (CURS) score at study enrollment had to be between 24 and 50.15 Subjects with severe unpredictable motor fluctuations; clinically relevant cardiac, hepatic, gastrointestinal, metabolic, renal, allergic, or psychiatric disorders; and/or intake of drugs that affect the dopaminergic system were not allowed to participate. Eighty-four patients finished the trial. We excluded 15 individuals (before unblinding) from the per-protocol analysis because of either premature termination not related to study medication (5 [10%] of budipine-treated patients and 2 [4%] of placebo-treated participants) or a major protocol violation (4 [8%] of budipine-treated individuals and 4 [8%] of placebo-treated subjects). There were no clinically relevant differences for the demographic data and clinical characteristics between both groups at baseline (Table 1).

DESIGN

We titrated the preexisting dopaminergic drug regimen to its optimum efficacy and tolerability (eg, onset of dyskinesia, vivid dreams, and cognitive deficits) according to the patients’ and treating physicians’ opinion within 4 weeks. Then, we kept the antiparkinsonian therapy stable for at least 4 weeks. A further 4-week screening period followed. Next, we slowly started titration of budipine from the initial application of 20 mg/d up to 60 mg/d, adding 10 mg/wk (Figure 2). Soon after that, participants took budipine, 20 mg 3 times daily, until the end of the trial for 11 weeks. We allowed reduction of budipine to 40 mg/d because of the onset of adverse effects. One blinded investigator determined the score of the patients. Another blinded independent physician controlled patients’ compliance, safety, and tolerability of budipine.

STATISTICAL ANALYSIS

We computed differences of the CURS score and its subscores of tremor (items [grade, 0–4]: arm [score right and left], head, and leg [score right and left]), rigidity (items [grade, 0–4]: arm [score right and left separately], neck, and leg [score right and left separately]), and bradykinesia (items [grade, 0–4]: bradykinesia [comparing slowness and poverty of movement in general], gait disturbance, posture, postural stability, and arising between baseline (score: [V−4 + V 0]/2) and the end of the trial (score: [V12 + V16]/2) in the budipine- and the placebo-treated groups (Figure 2).15,16 (V indicates visit; subscript numbers, number of the visit.) Then, we used the Wilcoxon rank sum test for comparison of both treatment arms. The P value was adjusted to .01 for multiple testing of CURS and its subscores.

Figure 1. Patient enrollment in the study.

Additional treatment with budipine in doses up to 20 mg 3 times daily significantly further improved parkinsonian symptoms compared with placebo in our trial. We confirm the results of another double-blind placebo-controlled study on the efficacy of budipine, 20 mg administered in the morning. This study showed a significant decrease of the CURS sum score and amelioration of rigidity, akinesia, and tremor in 29 patients undergoing levodopa and benserazide monotherapy. Two dropouts appeared in this earlier study.9 Previous open-label monocenter trials9,12 described the tremolytic efficacy of budipine with additionally performed long-term electromyographic recordings in 20 patients with PD (11 patients in one trial and 9 in another). Our results also confirm those of earlier predominantly open-label and retrospective studies on subjects with PD without a previous stable drug regimen and with an insufficiently titrated dopaminergic antiparkinsonian drug regimen. Przuntek and Muller11 provide a review. In contrast to those earlier studies, we used a higher dose of budipine, 20 mg 3 times daily, and titrated with certain selected dopaminergic drugs to an optimum response. Finally, our participants were enrolled in the study after receiving a stable dopaminergic drug regimen for 4 weeks. Despite this complex design, the addition of budipine further reduced parkinsonian symptoms. Therefore, we hypothesize that budipine, with its complex pharmacological profile, also influenced altered
In conclusion, our study demonstrates that budipine, 20 mg 3 times daily, provides an additional therapeutic benefit because of its hypothetic positive impact on altered nondopaminergic neurotransmission in patients with PD.

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From the Department of Neurology, Ruhr University of Bochum, Bochum, Germany (Drs Przuntek, Kraus, and T. Muller); Byk Gulden Pharmaceuticals, Constance, Germany (Drs Bliesath and Steinijans); the Department of Neurology, Ludwig Maximilian University of Munich, Munich, Germany (Dr Bütter); Parkinson Clinic, Wolfach (Dr Fuchs); the Department of Neurology, University of Bonn, Bonn, Germany (Dr Klockgether); the Department of Neurology, Barmbek General Hospital (Dr Lachenmayer), the Department of Neurosurgery, University of Hamburg (Dr D. Müller), and Lundbeck GmbH & Co (Dr Sgonina), Hamburg, Germany; Paracelsus-Elena Clinic, Kassel, Germany (Dr Ulm); and Josefstadt Neurological Outpatient Clinic, Vienna, Austria (Dr Volc). Drs Bittkau, Glass, Haller, Rathay, and Teshmar are in private practice in Germany.

Author contributions: Study concept and design (Drs Przuntek, Bliesath, Bittkau, Fuchs, Kraus, T. Muller, and Sgonina); acquisition of data (Drs Bittkau, Fuchs, Glass, Haller, Kraus, Lachenmayer, D. Muller, T. Muller, Rathay, Sgonina, Teshmar, Ulm, and Volc); analysis and interpretation of data (Drs Przuntek, Bittkau, Bliesath, Klockgether, Kraus, Sgonina, and Steinijans); drafting of the manuscript (Drs Przuntek, Bittkau, Bliesath, Kraus, T. Muller, Sgonina, and Steinijans); critical revision of the manuscript for important intellectual content (Drs Przuntek, Bliesath, Bittkau, Fuchs, Glass, Haller, Klockgether, Kraus, Lachenmayer, D. Muller, Rathay, Sgonina, Teshmar, Ulm, and Volc); statistical expertise (Drs Przuntek, Bliesath, T. Muller, and Steinijans); obtained funding (Drs Przuntek, Bittkau, Bliesath, Kraus, and Ulm); administrative, technical, and material support (Drs Przuntek, Bittkau, Fuchs, Glass, Haller, Klockgether, Kraus, D. Muller, Rathay, Sgonina, Ulm, and Volc); and study supervision (Drs Przuntek, Klockgether, Kraus, Lachenmayer, T. Muller, and Sgonina).

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Corresponding author and reprints: Horst Przuntek, MD, Department of Neurology, Ruhr University of Bochum, Gudrunstrasse 56, 44791 Bochum, Germany (e-mail: Horst.Przuntek@ruhr-uni-bochum.de).

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