Eur Arch Psychiatr Neurol Sci (1988) 237:298–303

European Archives of Psychiatry and Neurological Sciences

Terguride in Parkinsonism

A Multicenter Trial

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Summary. Terguride is an ergoline derivative with mixed agonistic/antagonistic dopaminergic activity. This led to a paradoxical suggestion that it is effective in the treatment of both schizophrenia and parkinsonism. A total of 65 in- or outpatients with parkinsonism mostly of vascular or idiopathic etiology were included in a 4-week, open, multicenter trial. Terguride was administered under an increasing dose schedule which was leveled off according to the clinical response. Mostly because of nausea, vomiting, and lack of improvement 25% of inpatients and 61% of outpatients were removed from the study. The average daily dose at the end of the trial was 4.2 mg, ranging from 1.0 to 5.5 mg. The average Simpson and Angus scale total score and performance in the Spiral Drawing Task improved significantly during the trial by 20% and 38% respectively. The following adverse effects were noted most frequently throughout the study (including those who withdrew): constipation (occurred in 42% of all ratings performed during the trial) drowsiness and nausea (16% each). Adverse circulatory effects were negligible. Psychotic symptoms, including depression, confusion, hallucinations, and paranoid syndrome, each occurred in 1 patient, i.e., at a lower rate than with other dopaminergic drugs. Scotopic electroretinograms in a subsample of 7 patients showed a significant transitory decrease in the B-wave amplitude at the end of the 1st week and a subsequent return to pretreatment values.

Key words: Parkinson's disease – Dopamine – Terguride – Electroretinography

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Introduction

Terguride is an ergoline derivative originally synthesized in the Research Institute of Pharmacy and Biochemistry (VÚFB) Prague (Zikán et al. 1972). It possesses dual (mixed agonistic/antagonistic) activity on the dopaminergic receptor. Preclinical studies in laboratory animals (rats, mice) indicated that the final effect on the receptor in various parts of the brain may be dissociated. A marked inhibitory effect of terguride on prolactin release and inhibition of the cataleptic effect of neuroleptics indicated stimulation of dopaminergic processes in tuberoinfundibular and nigrostriatal pathways, respectively; decrease of spontaneous locomotor activity, impairment of motor coordination, and inhibition of apomorphine-induced stereotypes indicated inhibition of dopaminergic processes in mesolimbic and mesocortical pathways (Krejčí et al. 1984; Wachtel and Dorow 1983). This led to a paradoxical suggestion, that terguride might be used for treatment of both schizophrenia and parkinsonism (Krejčí 1985).

Previous clinical trials demonstrated that terguride might have a beneficial effect in early (Suchý et al. 1986), as well as in advanced (Suchý et al. 1986; Bruecke et al. 1986) stages of Parkinson's disease.

The purpose of our study was to obtain information on the therapeutic efficacy, adverse effects, and the therapeutic range of terguride in less severe forms of parkinsonism. Taking into consideration the existence of the dopaminergic network in the bipolar cell layer of the retina (Nichols et al. 1967; Kramer 1971) we also studied the effects of terguride on the

scotopic electroretinogram (ERG). Since the main component of ERG, the B-wave, is generated in the bipolar cell layer (Dick and Miller 1978), we hypothesized that the B-wave amplitude might be affected by administration of terguride.

Subjects and Methods

A 4-week, open multicenter study was conducted with neurological patients, treated either on an inpatient or an outpatient basis.

Subjects. A total of 65 subjects (37 female, 28 male) were recruited in 6 centers (Table 1) after giving informed consent. Each patient underwent a thorough medical and neurological examination.

In 57 patients, symptoms of central vascular disease were found in addition to the symptoms of parkinsonism: atherosclerosis of the fundus vessels, axial and/or paraaxial symptomatology, asymmetry of reflexes, symptoms of pyramidal irritation, pseudobulbar syndrome, etc. Those findings were often accompanied by general symptoms indicating a risk of vascular lesions e.g., left ventricle hypertrophy, elongation of aorta, hypertension, gerontoxon, laboratory signs of disturbed cholesterol and/or lipid metabolism (e.g., HDL and LDL deviations). This suggested vascular lesions as the ethiological factor of parkinsonism in this subgroup of patients, although simple coexistence of atherosclerosis and idiopathic parkinsonism remained as a possible alternative. The strict criteria for idiopathic parkinsonism were fulfilled in 6 patients, and in 2 patients the parkinsonism was of toxic origin.

The age range of the experimental population was 31 to 80 years, average 67 years. The dysfunction was of mild to medium severity corresponding to stages I to III according to Hoehn and Yahr (1967) and with an average duration of 3.5 $\pm$ 0.3 (mean $\pm$ SE). Patients treated with L-dopa or neuroleptics, as well as patients with serious somatic diseases, epilepsy, a history of psychosis including amentia, or patients who were pregnant or lactating were not included in the study.

Most of the patients had been treated with antiparkinson drugs prior to the study; 25 patients were switched from anticholinergic drugs, 15 from amantadin, and 12 from other antiparkinson drugs (but not L-dopa – see exclusion criteria). During the trial, no antiparkinson drugs other than terguride were administered. The ERG was recorded in 10 subjects in center No. 1. only.

Experimental Medication. Terguride was administered with meals according to a fixed-changing dosage schedule starting with a single dose of 0.5 mg per day, with a daily increment of 0.5 mg, until the symptoms ameliorated or adverse effects causing discomfort appeared.

Assessment of Change. Clinical symptomatology was evaluated at pretreatment and then once weekly by means of the Simpson and Angus rating scale (Simpson and Angus 1970), the Spiral Drawing Task (Terziivanov et al. 1982), and Clinical Global Impressions (Guy 1976).

Scotopic ERG was recorded on the same occasion according to the method of Balík (1971) using averaging of series of 5 stimuli. Three series of stimuli with increasing stimulus level (light energy) between series were used. The ERGs were evaluated under blind conditions.

Table 1. Numbers of patients studied at the different centers (outpatient departments marked by [a])

Center	City	Included	Finished
1	Prague 5	13	11
2	Vlašim	13	11
3	Kolín	10	6
4	Kladno	11	7
5[a]	Prague 6	7	4
6[a]	Prague 5	11	3
		65	42

Blood pressure and heart rate were monitored throughout the whole study. Routine laboratory tests (BSR, blood sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase, bilirubin, potassium, urea, blood count, urinalysis) were documented at pretreatment and at termination of the study.

Statistical Evaluation. Student's *t*-test for paired observations (comparison to pretreatment) was used for statistical evaluations or rating scales data. The statistics for a particular assessment period were computed for all patients remaining in the study for that period. The ERG data were evaluated by two-way ANOVA with stimulus energy and the recording period as sources of variance and additionally with Student's *t*-test in a way analogous to the rating scales data.

Linear regression analysis (simple and stepwise) was used for prediction of a therapeutic response on the basis of pretreatment data. As a measure of improvement, the Improvement Index according to Rakús et al. (1984) was used. Using this index meant that (a) the same difference score was given higher weight when the space for the change was smaller (i.e., a change from 4 to 3 means lower improvement than from 2 to 1) and (b) a substantial drop in symptomatology in a few items was regarded as better improvement than a small decrease in symptomatology in many items (although the difference in total score may be the same).

Results

Course of the Study

Some 23 patients were removed from the study. Treatment was stopped in the 2nd week due to nausea or vomiting in 6 patients, clinical deterioration in 2, insomnia in 2, dizziness in 1, depression in 1, constipation in 1; in the 3rd week due to clinical deterioration in 1, amentia in 1, hallucinations in 1, dizziness in 1, constipation in 1 and 2 patients appeared too late for clinical assessment; and in the 4th week due to delusions in 1, vomiting in 1, and athetoid movements and hypersalivation in 1. The data on all patients who remained in the trial until the evaluated assessment period were used for statistical evaluation of clinical assessments.

Also, 30 patients received additional medication during the study, with an average frequency of 2.8

additional medications per patient in this group. Thus, 30 were treated with vasodilatators, 11 with cardiac glycosides, 6 with antihypertensive agents, and 28 with other drugs, which were not among the exclusion criteria. The dosage of terguride leveled off at the end of week 2 at an average daily dose of 4.2 ± 0.2 mg (mean $\pm$ SE).

Therapeutic Efficacy

The average Simpson and Angus total score dropped significantly during the trial from 16.0 ± 0.9 (mean $\pm$ SE) to 13.0 ± 1.2 points ($P < 0.001$) (Fig. 1). The best improvement rate (with $P < 0.001$) occurred in the following items (baseline and final scores means $\pm$ SEs in brackets): gait (1.8 ± 0.1, 1.5 ± 0.2), arms dropping (1.8 ± 0.1, 1.5 ± 0.2), elbow rigidity (1.4 ± 0.1, 1.3 ± 0.1), leg swing (2.0 ± 0.1, 1.9 ± 0.2), and tremor (2.0 ± 0.1, 1.7 ± 0.2). Similarly, there was a significant improvement in performance in the Spiral Drawing Task, with an average increase of whorls per second (sum of both hands) from 0.29 ± 0.02 to 0.40 ± 0.03 at the end of week 4 (Fig. 1).

The Global Improvement score of Clinical Global Impressions at the time the patient left the trial (regardless of whether at the end or prematurely) showed bimodal distribution, with most patients rated as "unchanged or worse" or "moderate improvement" (Table 2).

Prediction of Therapeutic Outcome

There was a general impression during the trial that the therapeutic response in the more severe cases was less favorable than in the less severe ones. Therefore, regression analysis was done to estimate whether the Improvement Index on the termination day could be predicted on the basis of pretreatment data. Using the total score of the Simpson and Angus rating scale at pretreatment as a predicting variable and the Improvement Index as the predicted variable, a significant negative regression ($P = 0.001$) with multiple $r = 0.4$ was found, which confirmed the clinical observation (Fig. 4).

Adverse Effects

Adverse effects were noted most frequently for the following items: constipation (in 42% of all ratings performed during the trial), drowsiness (in 20% of ratings), and nausea (in 16% of ratings). The highest intensity of adverse effects was noted for the same three items. The scores of those items significantly increased during treatment ($P < 0.001$). The peak occurred mostly in the 1st week of the study, although

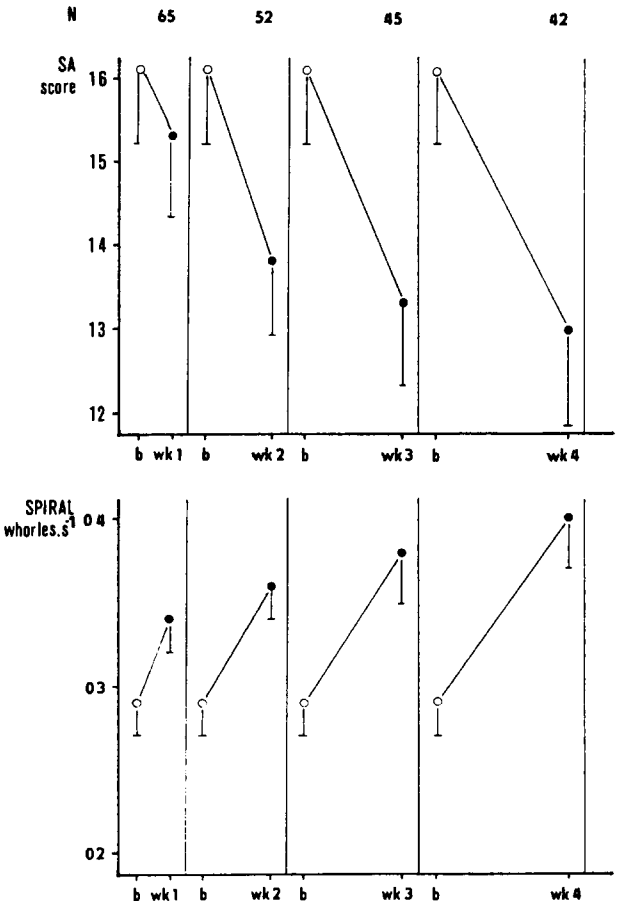

Fig. 1. Changes of Simpson and Angus scale total score (SA) and Spiral Drawing Task during the trial (mean $\pm$ SE). Due to decreasing N *(top)* caused by patients' withdrawing, a separate *t*-test was computed for each week of the trial, including only cases remaining in the study. This resulted in slightly different baseline values for each computation. Therefore, the data for particular weeks are shown separately (b = baseline, wk = week) from left to right

Table 2. Clinical Global Impression rating at the time of the drug discontinuation (those withdrawing included)

Unchanged or worse	29
Minimal improvement	9
Moderate improvement	22
Marked improvement	2
Missing data	3
Total	65

for constipation it was in the 2nd week. The increase in orthostatic collapse score was less pronounced, nevertheless significantly different from pretreatment. The scores of other adverse effects did not increase significantly during the trial. In 80% of patients, the adverse effects did not interfere severely with their activities. In the remaining 20%, the ad-

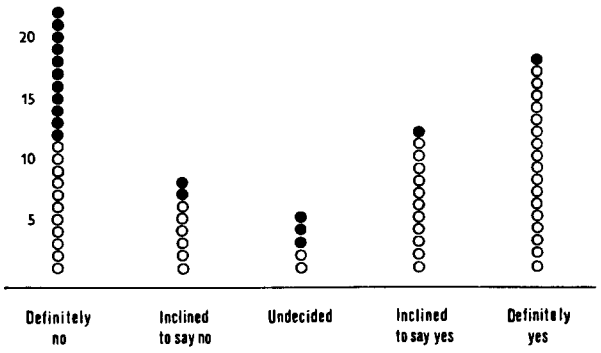

Fig. 2. Distribution of raters' responses to the question: "given the choice, would you continue this subject on his study medication?" Each dot represents one subject. *Full dots:* patients treated in outpatient departments. *Empty dots:* patient treated in hospital wards

verse effects outweighted the therapeutic effect. Severe adverse circulatory effects were not observed.

Willingness to Continue the Study Medication

The raters were asked whether they would continue the given patient on the study medication after the trial. Similarly, as in the Clinical Global Impressions, the answer to this question showed a bimodal distribution, dividing the patients into two fairly distinct groups (Fig. 2).

Brief Physical Routine

Statistical analysis did not reveal any significant changes in blood pressure and heart rate during the study.

Routine Laboratory Tests

There was no clinically significant change in the values of any of these tests during the trial.

Changes in ERG

The ERG was recorded in 10 patients in center No 1 only. Due to movement artifacts, recordings of 3 subjects were removed from the analysis. Analysis of the ERGs of the remaining 7 patients showed significant effects of stimulus energy in all recording periods ($P<0.05$) and a significant ($P<0.05$) decrease in the ERG B-wave amplitude at two highest stimulation levels at the end of week 1 ($P<0.05$), with a return to pretreatment values at the end of week 2 (Fig. 3). Week 3 recordings gave similar results to those of week 2, i.e., no significant differences from pretreatment were observed, however, a trend to exceed pretreatment values was apparent. Week 4 data

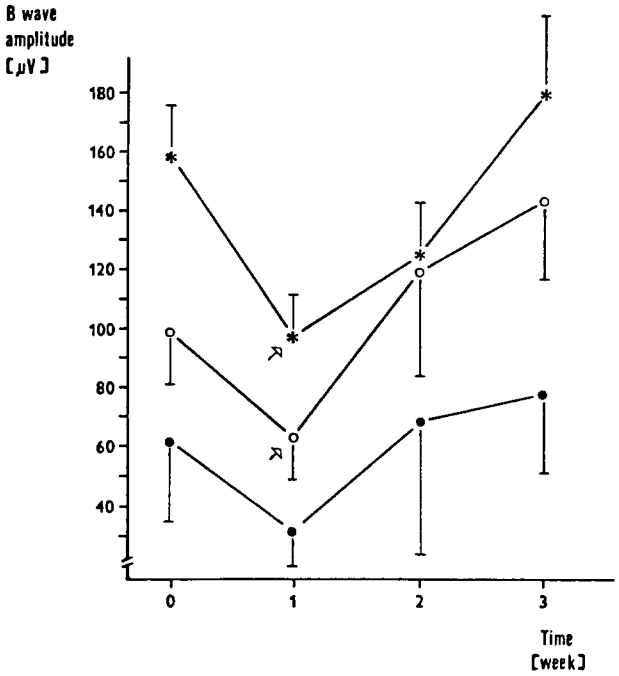

Fig. 3. Time course of electroretinogram B-wave amplitude during treatment with terguride. The curves ●, ○, and * represent 0.01, 0.1, and 1.0 stimulation (light energy) levels respectively. At the two highest stimulation levels, the B-wave amplitude at the end of week 1 *(arrow)* was significantly lower than at pretreatment ($P<0.01$).

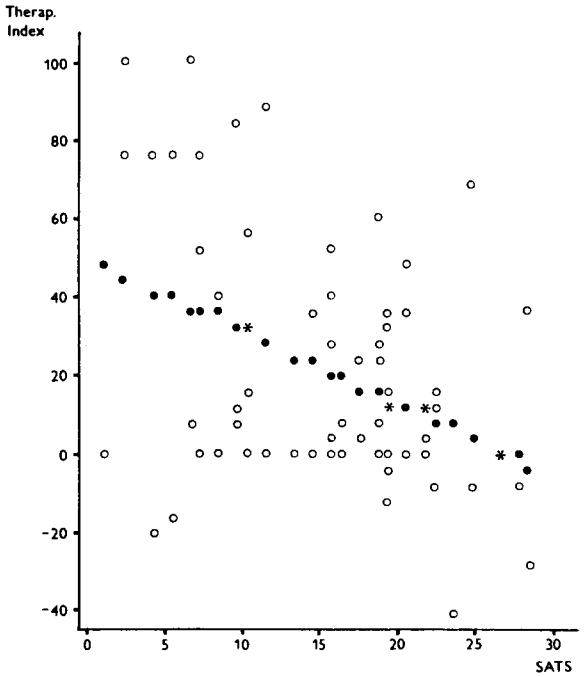

Fig. 4. Prediction of the therapeutic outcome on the basis of pretreatment symptomatology. Total score of Simpson and Angus rating scale at pretreatment (SATS) plotted against the Therapeutic Index (according Rakus et al. 1984) at terminal assessment. ● = values predicted on the basis of the regression equation, ○ = observed values. Each point represents one or more (*) subjects. Correlation coefficient $r = 0.4$, $P = 0.001$

were not included in the analysis, due to patient withdrawal.

Discussion

Preclinical studies demonstrated a dual effect of terguride upon the dopaminergic receptor. Our results show that in a clinical trial with subjects suffering from parkinsonism the agonistic properties of the drug clearly prevail. Terguride significantly improved all three main characteristics of the syndrome: rigidity, tremor, and bradykinesia. The therapeutic efficacy was low to moderate – most of the patients were moderately improved after 4 weeks of treatment.

The dosage schedule used in this study was derived from previous experience with terguride administration to patients with hyperprolactinemia, where daily doses up to 10 mg/day were well-tolerated (Marek et al. 1987). Taking into consideration possible dopaminergic supersensitivity in parkinsonism, the dose was increased gradually. The fact that it was mostly during the first 2 weeks that patients withdrew indicates that some patients need an even more cautious treatment schedule.

It is apparent from the Table 1 that the highest withdrawal rate was in center 6, which is an outpatient department. Whereas the proportion of the patients who finished the study was 75% in the hospital wards (centers 1 to 4), only 39% finished in the outpatient departments (centers 5 and 6). The difference was statistically significant ($\chi^2 = 7.21$, $P < 0.01$) and indicated that immediate adjustment of the dosage at the earlierst stage of treatment-related symptom development is necessary. Without this feedback, the acceptance of the drug by the patient is most likely to be poor. The same is reflected in willingness of the doctors to continue the study medication (Fig. 2).

Despite high dosage, the ratio of therapeutic to adverse effects was favorable in 2/3 of the patients, which is better than with other drugs, e.g., lisuride. This is mainly due to a lower incidence of adverse circulatory effects, which were fairly frequent in a previous trial with lisuride (Filipová et al. 1987).

For ethical reasons we did not use any pretreatment wash-out period. Therefore, the baseline level of extrapyramidal symptomatology was influenced by previous treatment in most patients, leaving little space for further improvement.

The improvement rate in our study (approximately 20%) was higher than in that of Suchý et al. (1986) (approximately 10% in subgroups I and II which were similar to the population of this trial). In contrast to the conclusion of Suchý et al. (1986) this difference could indicate that the response to terguride may be dose-related, since the dosage in our study was double that of Suchý et al., and in both studies, terguride was used as monotherapy. A comparison with the results of Bruecke et al. (1986) is difficult due to the different population studied (an advanced stage of the disease and simultaneous therapy with L-dopa preparations).

Experience with administration of terguride to selected patients for several months after the completion of the experimental protocol indicated that despite a favorable response during the trial, the clinical symptomatology in some of them continued to deteriorate. It is not possible to decide at this stage whether it is a consequence of development of tolerance or of further progression of the disease.

The biphasic effect of terguride on the ERG can be explained either by receptor sensitivity adaptation during therapy, or by a dose-dependent dual effect (in 6 out of 7 patients whose ERGs were analyzed, the daily dosage at the end of week 2 was 0.5 mg higher than at the end of week 1).

The results of our study with terguride confirm the expectations and indicate that further development of this drug is substantiated.

Acknowledgement. The authors wish to express their thanks to Dr. Jana Dvořáková for excellent technical assistance and to Dr. Barbara Andersen for help with the preparation of the manuskript.

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Received September 28, 1987