Therapeutic Efficacy of Beta-Adrenergic Blocking Agents in Parkinsonian Tremor

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Introduction

For the past 20 years, drug therapy of Parkinson disease has centered around high-dose oral substitution of levodopa. Because of growing awareness of the shortcomings and late complications of levodopa therapy it can no longer be considered a universal therapeutic concept providing optimal control of symptoms in every parkinsonian patient in every stage of disease. To achieve optimal therapy of parkinsonism, the clinician must differentiate subtypes of the disease based on differences in symptoms (Table I).[1]

Especially in the tremor-dominant type (type 3), oral levodopa substitution alone often fails to control symptoms adequately. Based on a number of reports indicating a positive influence of beta-adrenergic blocking agents on parkinsonian tremor,[2-7] as well as of their ineffectiveness,[8-10] we further evaluated the efficacy of combined treatment of tremor-dominant Parkinson disease with levodopa and beta-adrenergic blocking agents.[11,12]

Table I
Clinical subtypes of Parkinson disease (Gerstenbrand and Poewe[1]).

Type 1	Equivalence type (akinesia-rigidity-tremor)
Type 2	Akinesia-rigidity type
Type 3	Tremor-dominant type
Type 4	Parkinsonism with pronounced depressive psychosis
Type 5	Parkinsonism with pronounced vegetative symptoms (borderline cases of Shy-Drager syndrome)
Type 6	Parkinsonism with pronounced optomotor disturbances (borderline cases of Steele-Richardson-Olszewski syndrome)
Type 7	Parkinsonism with dementia (dementia type; borderline cases of Parkinsonism-dementia-ALS-complex)

Material and Methods

Twenty-five patients with tremor-dominant Parkinson disease of at least one year's duration were selected according to the criteria of obtaining insufficient control of tremor with levodopa alone and having no internal contraindications to therapy with beta-blocking substances. The disease was of the idiopathic type in all cases. Patients who had undergone bilateral stereotactic operations were excluded as well as those who had experienced previous psychotic reactions or dyskinesias while on levodopa. The basic levodopa therapy was kept constant for at least three months prior to the study, and no concomitant antiparkinsonism medication was given during the study.

In the first group of ten patients (six men, four women; mean age, 62 years) bupranolol was given orally in addition to levodopa in a double-blind crossover study with placebo. The dosage of bupranolol was increased from 100 mg/day to 200 mg/day during the four-week study period.

In a second group of ten patients (five men, five women; mean age, 64 years) propranolol was administered orally along with levodopa in an analogous study design. Dosage of propranolol was kept between 80 and 120 mg/day.

Five patients were treated with a combination of levodopa and a new compound with potent beta-adrenergic blocking properties of prolonged duration, LT 31-200 (Sandoz Corporation, Basle, Switzerland), which was given orally in a single morning dose of 2 to 8 mg.

A modified Webster scale, a patient's self-rating scale, and a modified Northwestern University disability scale were used to evaluate symptoms during the study. Motor performance was assessed in a test battery of five subunit tasks, and the emotional state was evaluated by means of the Hamilton scale and the 100-mm test.

Results

The effects of combined treatment with levodopa and bupranolol or propranolol on tremor, rigidity, akinesia, and the emotional condition are displayed in Figures 1 to 5. Tremor was markedly reduced in six of the ten patients receiving bupranolol and seven of the ten patients receiving propranolol (Figure 1). Although some individual improvement in rigidity and akinesia occurred (Figures 2 and 3), most patients on either regimen did not show improvement of these symptoms. Emotional condition improved remarkably in three patients in group one (Figure 4, patients 1, 4, and 6), while four patients had slight improvement. In group two, eight of ten patients improved in their emotional condition (Figure 5).

The overall improvement of both groups is displayed in Figures 6 and 7, revealing 75% to 100% improvement in eight patients in each group. All patients had at least 50% improvement.

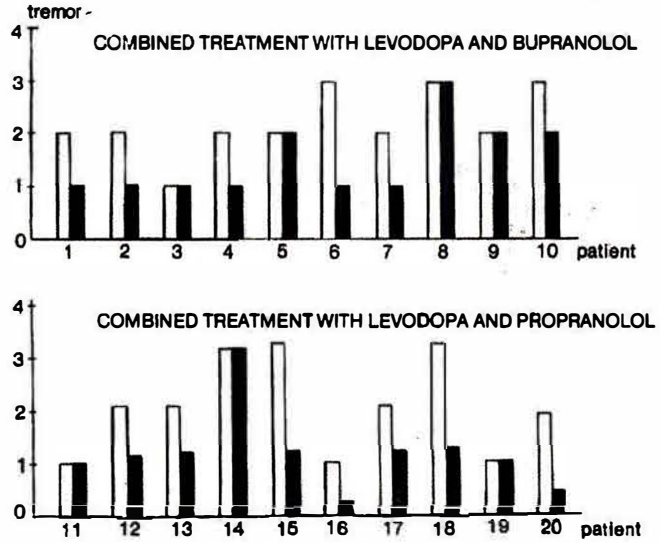

Figure 1. Tremor score in 20 patients with tremor-dominant Parkinson disease treated with a combination of levodopa and a beta-adrenoceptor antagonist (□ = before addition of beta-adrenoceptor antagonist; ■ = four weeks after addition of beta-adrenoceptor antagonist).

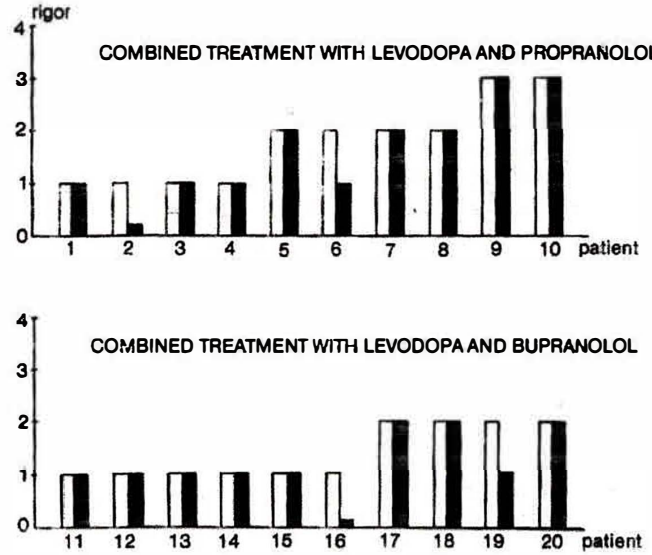

Figure 2. Rigidity score in 20 patients with tremor-dominant Parkinson disease treated with a combination of levodopa and a beta-adrenoceptor antagonist (□ = before addition of beta-adrenoceptor antagonist; ■ = four weeks after addition of beta-adrenoceptor antagonist).

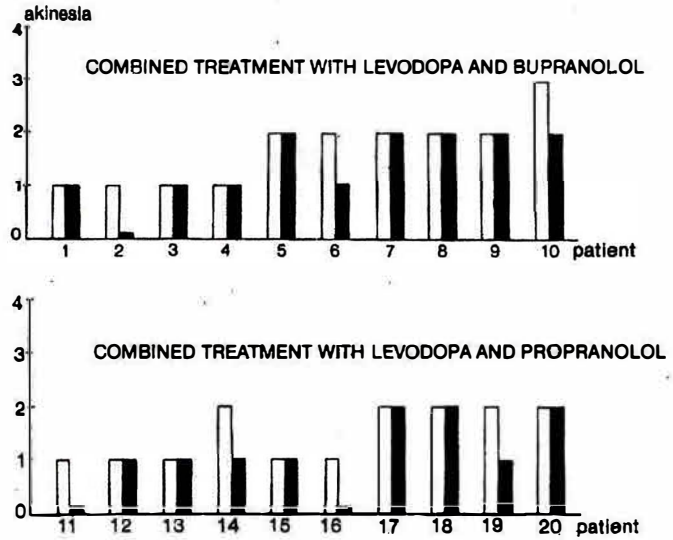

Figure 3. Akinesia score in 20 patients with tremor-dominant Parkinson disease treated with a combination of levodopa and a beta-adrenoceptor antagonist (□ = before addition of beta-adrenoceptor antagonist; ■ = four weeks after addition of beta-adrenoceptor antagonist).

Currently we are investigating the beta-adrenoceptor antagonist LT 31-200 in combination with levodopa for tremor-dominant Parkinson disease. The substance blocks beta-1 and beta-2 adrenoceptors and has a longer duration of action than propranolol or bupranolol. Thus it is possible to conduct oral treatment with one dose per day in the morning. Because the drug's beta-adrenergic blocking effects on the cardiovascular system are about ten times more potent than those of pindolol or propranolol, low doses can be used.

The results of a four-week treatment phase are available for five patients, all of whom had a significant reduction of tremor scores (Figure 8). At the same time, motor performance scores, obtained by adding the scores of the motor test battery, showed a marked increase (Figure 9).

Side effects of the combined therapies in all 25 patients were negligible, owing to a careful selection of subjects. Eight patients complained of mild headache and vertigo at the beginning of the study, which disappeared despite continuing the medication. A substantial fall in blood pressure or pulse rate was not observed.

Fifteen of the 25 patients continued the combination therapy with levodopa and the respective beta-adrenoceptor antagonist for three to ten months after the end of the trial. In four the therapeutic effect declined and could not be restored by increasing the dosage of the beta-adrenoceptor antagonist.

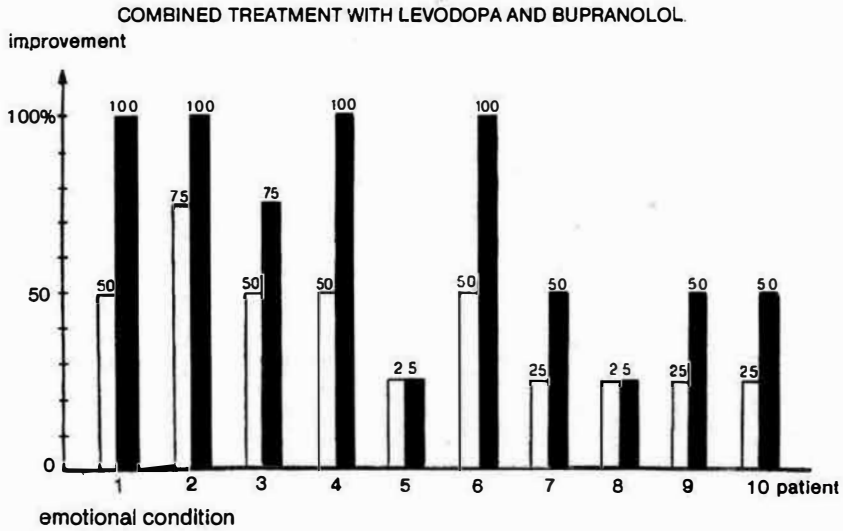

Figure 4. Emotional condition in ten patients with tremor-dominant Parkinson disease treated with a combination of levodopa and bupranolol (□ = before addition of bupranolol; ■ = four weeks after addition of bupranolol).

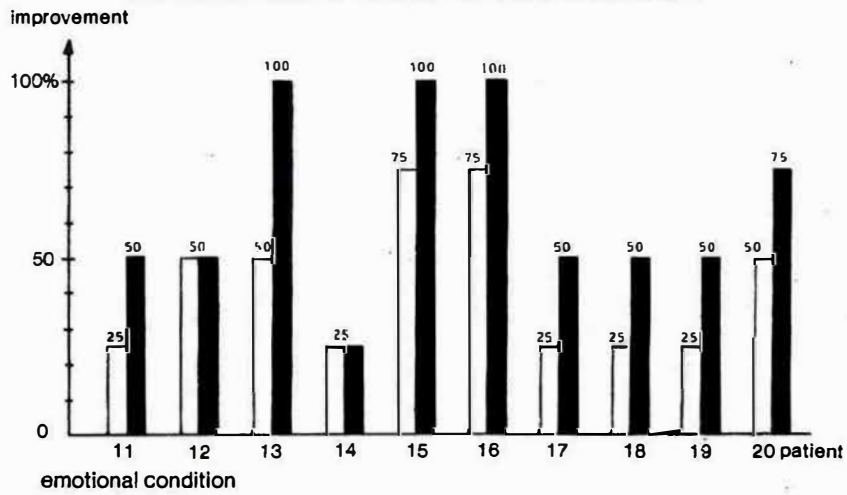

Figure 5. Emotional condition in ten patients with tremor-dominant Parkinson disease treated with a combination of levodopa and propranolol (□ = before addition of propranolol; ■ = four weeks after addition of propranolol)

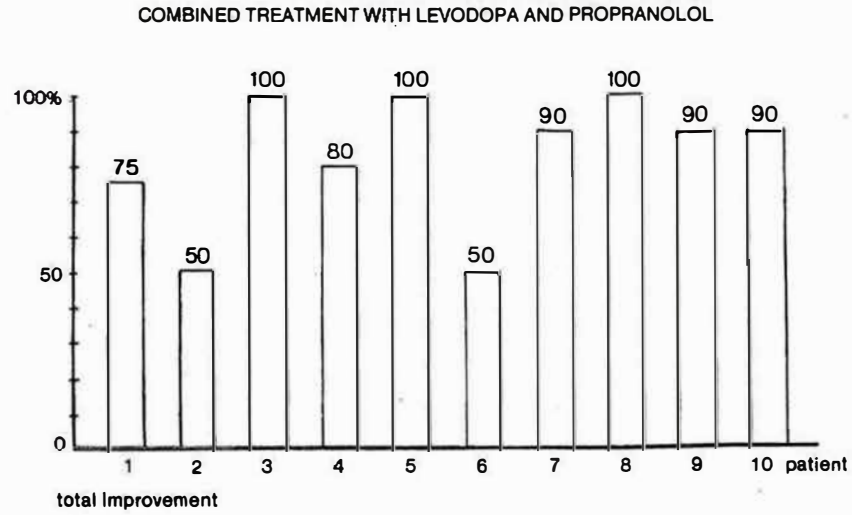

Figure 6. Overall improvement in ten patients with tremor-dominant Parkinson disease treated with a combination of levodopa and bupranolol (□ = before addition of bupranolol; ■ = four weeks after addition of bupranolol). Symptom and test scores were taken as 100% at the beginning of the trial.

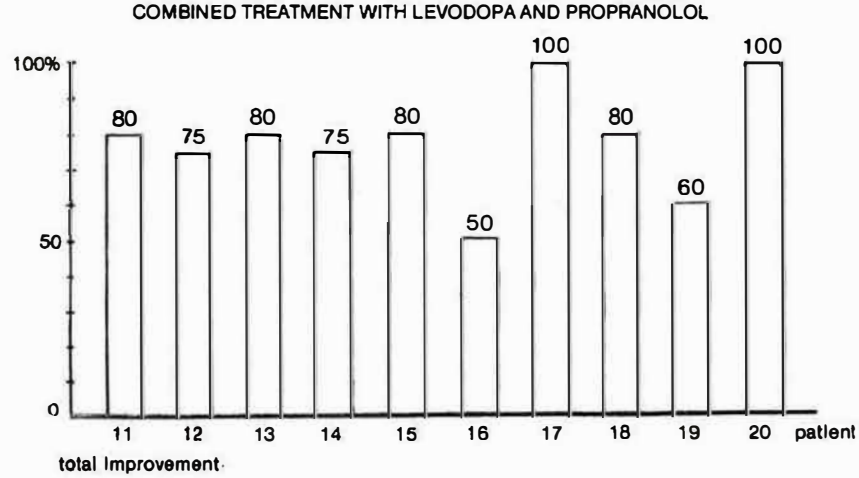

Figure 7. Overall improvement in ten patients with tremor-dominant Parkinson disease treated with a combination of levodopa and propranolol (□ = before addition of propranolol; ■ = four weeks after addition of propranolol). Symptom and test scores were taken as 100% at the

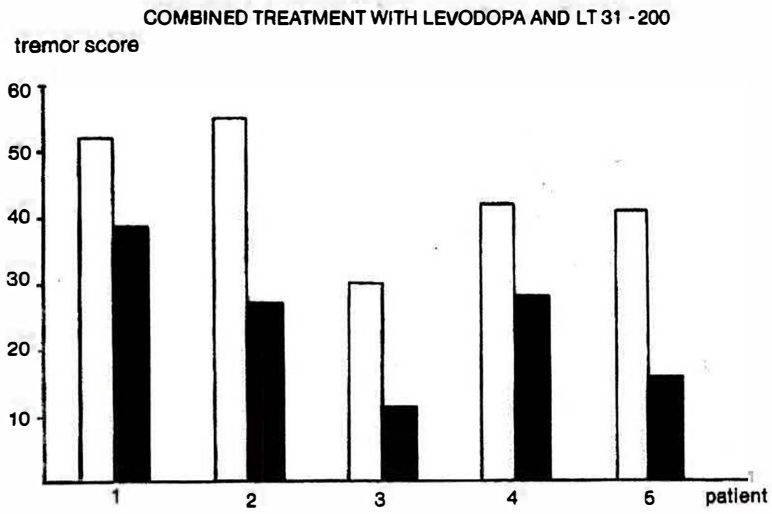

Figure 8. Tremor scores in five patients with tremor-dominant Parkinson disease treated with levodopa and LT 31-200 (□ = before addition of LT 31-200; ■ = four weeks after addition of LT 31-200).

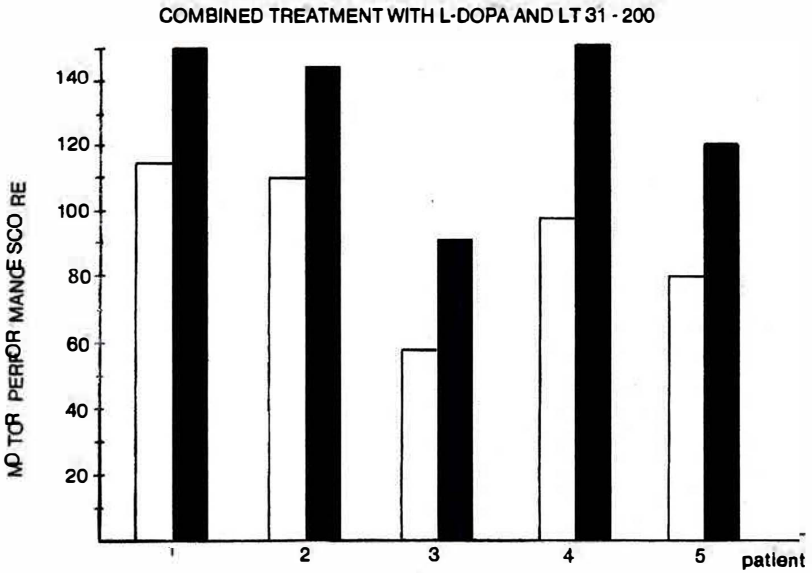

Figure 9. Motor performance scores in five patients with tremor-dominant Parkinson disease treated with levodopa and LT 31-200 (□ = before addition of LT 31- 200; ■ = four weeks after addition of LT 31-200).

Discussion

Our positive results obtained in treatment of tremor-dominant Parkinson disease by a combination of levodopa with beta-adrenoceptor antagonists correspond well with the results of others.[4,6,13,14] They demonstrate that the combination of levodopa with a beta-adrenoceptor antagonist provides better control of parkinsonian tremor than does levodopa alone. Additionally, the combination exerts a positive influence on the emotional condition. In individual cases, even rigidity and akinesia responded. The overall condition of the majority of patients improved. The question of long-term effectiveness of combined treatment with levodopa and a beta-adrenoceptor antagonist cannot yet be answered from our material, although eight of our patients sustained improvement over ten months.

The mechanism by which beta-adrenoceptor antagonists improve parkinsonian tremor is not yet clear. A central site of action is postulated, but not yet proved. The anxiolytic property of beta-adrenoceptor antagonists does not suffice to explain amelioration of tremor to the degree observed in our patients. Peripheral mechanisms in the tremor control by beta-adrenergic antagonists have been suggested.[15]

Summary

Twenty-five carefully selected patients with tremor-dominant Parkinson disease were selected for an investigation of combination therapy with levodopa and a beta-adrenoceptor antagonist. None had achieved satisfactory control with levodopa alone. The beta-adrenergic blocking agents used in this study were: bupranolol, ten patients; propranolol, ten patients; and a new drug, LT 31-200, five patients. The three regimens were equally effective. Although akinesia and rigidity were not improved in most cases, control of tremor was much better than had been achieved with levodopa alone. Improvements in emotional state and overall condition were observed with the combination of levodopa and a beta-adrenoceptor antagonist. Owing to careful selection of patients, side effects were minimal. We conclude that combined treatment with levodopa and a beta-adrenergic antagonist is effective therapy for tremor-dominant Parkinson disease.

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Eficacia terapéutica de los agentes bloqueantes beta-adrenérgicos sobre el temblor parkinsoniano

Sumario

Se eligieron veinticinco pacientes con la enfermedad de Parkinson, en estadío de temblor dominante, cuidadosamente seleccionados, para una investigación de terapia combinada, usando levodopa y un antagonista beta-adrenoceptor. Ninguno de ellos había logrado un control satisfactorio con el uso exclusivo de levodopa. Los agentes bloqueantes beta-adrenérgicos usados en este estudio fueron: bupranolol, diez pacientes; propranolol, diez pacientes; y una droga nueva, LT 31–200, cinco pacientes. Los tres régimenes fueron igualmente efectivos. A pesar de que la acinesia y la rigidez no se mejoraron en la mayoría de los casos, se mejoró el control del temblor mucho más que lo que se había logrado con el uso exclusivo de levodopa. Se observaron mejoras en el estado emocional y la condición general con la combinación de levodopa y un antagonista beta-adrenoceptor. Debido a la selección cuidadosa de los pacientes, los efectos secundarios

fueron mínimos. Llegamos a la conclusión de que el tratamiento combinado de levodopa y un antagonista beta-adrenérgico constituye una terapia efectiva en la enfermedad de Parkinson en el estadío de temblor dominante.

Therapeutische Wirksamkeit von Betarezeptorenblockern beim Parkinsontremor

Zusammenfassung

25 sorgfältig ausgewählte Patienten mit von Tremor gekennzeichneter Parkinsonscher Erkrankung sind für eine Untersuchung ausgesondert worden, in der eine Kombinationstherapie von Lävodopa und einem Beta-Adrenorezeptor-Antagonist angewandt wurde. In keinem der Fälle hatte die Behandlung mit Lävodopa allein befriedigende Resultate ergeben. Die folgenden beta-adrenergischen Blocker wurden in dieser Untersuchung benutzt: Bupranolol, zehn Patienten; Propranolol, zehn Patienten; und eine neue Droge, LI 31–200, fünf Patienten. Alle drei Behandlungsweisen waren in gleichem Masse erfolgreich. Obwohl Akinesie und Rigidität in den meisten Fällen nicht verbessert wurden, war die Kontrolle des Tremors wesentlich besser als die durch Lävodopa allein hervorgerufene Kontrolle. Auch Verbesserungen im Gefühlszustand und im allgemeinen Befinden konnten bei der Anwendung der Lävodopa und Beta-Adrenorezeptor-Antagonisten-Kombination beobachtet werden. Dank der sorgfältigen Auswahl der Patienten waren Nebenerscheinungen minimal. Wir folgern hieraus, dass die Kombinationsbehandlung mit Lävodopa und beta-adrenergischen Antagonisten eine wirksame Therapie für durch Tremor gekennzeichnete Parkinsonsche Erkrankung darstellt.

Efficacité thérapeutique des agents bêta-adrénergiques bloqueurs sur le tremblement parkinsonien

Sommaire

Vingt-cinq patients atteints de la maladie de Parkinson avec tremblements dominants ont été choisis avec soin pour faire des recherches sur une thérapie qui comprendrait la levodopa et un antagoniste des bêta-adrénocepteurs. Aucun de ceux-ci n'ont atteint un contrôle satisfaisant avec la seule aide de la levodopa. Les agents bêta-adrénergiques bloqueurs utilisés dans cette étude étaient: le bupranolol, sur dix patients; le propranolol, sur dix

patients; et une nouvelle drogue, LT 31–200, sur cinq patients. Les trois régimes étaient également efficaces. Bien que l'akinésie et la rigidité n'aient pas été améliorées dans la plupart des cas, le contrôle des tremblements était bien meilleur que celui atteint par la levodopa prise seule. Des progrès dans l'état émotionnel et la condition en général ont été observés lorsque la levodopa était administrée en conjonction avec un antagoniste des bêta-adrénocepteurs. A cause du soin pris dans le choix des patients, les effets secondaires ont été minimes. Nous concluons qu'un traitement à la levodopa associé à un antagoniste des bêta-adrénocepteurs est une thérapie efficace pour la maladie de Parkinson avec tremblements dominants.

Efficacia terapeutica del blocco beta-adrenergico del tremore parkinsoniano

Riassunto

Per un'indagine sulla terapia di levodopa associato ad un antagonista beta-adrenocettore sono stati accuratamente selezionati venticinque malati del morbo di Parkinson con tremore predominante. Sono stati usati in questa ricerca i seguenti agenti bloccanti beta-adrenergici: bupranolol, dieci malati; propranolol, dieci malati; ed un nuovo farmaco, LT 31–200, cinque malati. I tre regimi si sono dimostrati ugualmente efficaci. Benchè l'acinesia e la rigidità non fossero migliorate nella maggioranza dei casi, il controllo del tremore era molto migliore di quello ottenuto col solo levodopa. Sono stati osservati miglioramenti nello stato emozionale e nelle condizioni generali con l'uso di un'associazione di levodopa ed un antagonista beta-adrenocettore. A causa della selezione accurata dei soggetti erano minimi gli effetti collaterali. Si puó concludere che il trattamento di levodopa associato ad un antagonista beta-adrenocettore è una terapia efficace per il morbo di Parkinson con tremore predominante.

Eficácia terapêutica dos agentes bloqueadores beta-adrenérgicos no tremor parkinsoniano

Sumário

Vinte e cinco pacientes, cuidadosamente selecionados, apresentando doença de Parkinson com tremor dominante, foram escolhidos para um estudo no qual foi utilizada uma terapia combinada de levodopa e um antagonista beta-adrenoceptor. Nenhum deles obteve um controle satisfatório com o uso de levodopa apenas. Os agentes de bloqueio beta-adrenérgicos usados neste estudo foram: bupranolol (em dez pacientes), propranolol (em dez pacientes), e uma nova droga LT 31–200 (em cinco pacientes). Os três tratamentos foram igualmente eficazes. Embora a acinésia e rigidez não tenham melhorado na maioria dos casos, o controle do tremor foi superior ao obtido com levodopa apenas. Melhoras do estado emocional e da condição geral foram observadas combinando-se levodopa e um antagonista beta-adrenoceptor. Devido à cuidadosa seleção dos pacientes, os efeitos secundários foram reduzidos ao mínimo. Concluímos assim que o tratamento combinado de levodopa e um antagonista beta-adrenérgico é uma terapia efetiva para a doença de Parkinson com tremor dominante.

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